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Jon W Dudas

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Docket No.: 59104US002

Transmittal f Provisional Application

Mail Stop Provisional Patent Application
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Inventor(s): Tushar Kshirsagar, Woodbury, Minnesota; and Gregory Lundquist Jr., Eagan, Minnesota.

Title: HYDROXYLAMINE SUBSTITUTED IMIDAZOQUINOLINES

1. ☒ Enclosed is the above-identical new provisional application for patent under 35 USC § 111(b)(1). It includes:
   96 Pages of Text
   0 Sheets of Drawings
2. ☐ Enclosed is an executed Assignment to 3M Innovative Properties Company and a completed Assignment Recordation Cover Sheet.
3. ☐ This invention was made under a contract with an agency of the U.S. Government:
   Agency: _____
   Contract No. _____
4. ☒ Correspondence Address: Dean A. Ersfeld
   Office of Intellectual Property Counsel
   3M Innovative Properties Company
   P.O. Box 33427
   St. Paul, Minnesota 55133-3427
5. ☒ Please charge the $160.00 filing fee under 37 CFR § 1.16(k) to Deposit Account No. 13-3723. One copy of this sheet marked duplicate is also enclosed.
6. ☒ Please charge to Deposit Account No. 13-3723 any fees under 37 CFR §§ 1.16 and 1.17, which may be required to file and during the entire pendency of this application. This authorization includes the fee for any necessary extension of time under 37 CFR § 1.136(a). To the extent any such extension should become necessary, it is hereby requested.
7. ☒ Enclosed is a return receipt postcard.

Respectfully submitted,

14 NOVEMBER 2003
Date

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Filing of Papers and Fees by Express Mailing

Pursuant to 37 CFR § 1.10, this application and the documents and fees listed on this transmittal letter are being deposited on the date indicated below with the United States Postal Service "Express Mail Post Office to Addressee" service addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450

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HYDROXYLAMINE SUBSTITUTED IMIDAZOQUINOLINES

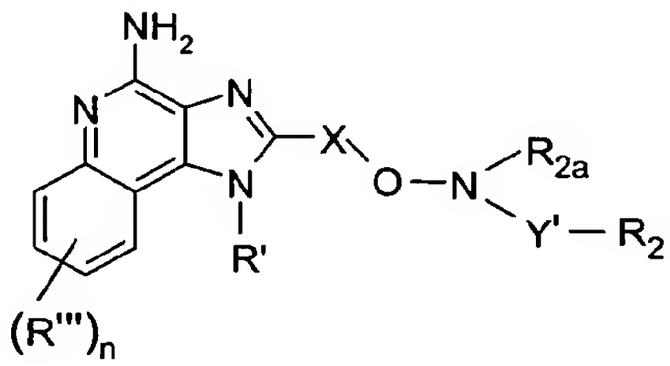
BACKGROUND

There has been a major effort in recent years to find compounds that modulate the immune system. Examples of such compounds, which have demonstrated cytokine inducing and immunomodulating activity, are disclosed by U.S. Patent Nos. 4,689,338; 4,929,624; 5,266,575; 5,268,376; 5,352,784; 5,389,640; 5,446,153; 5,482,936; 5,494,916; 5,756,747; 6,110,929; 6,194,425; 6,331,539; 6,376,669; 6,451,810; 6,525,064; 6,545,016; 6,545,017; and 6,573,273; and PCT Publications WO 02/46188, WO 02/ 46189; WO 02/46190; WO 02/46191; WO 02/46192; and WO 02/46193.

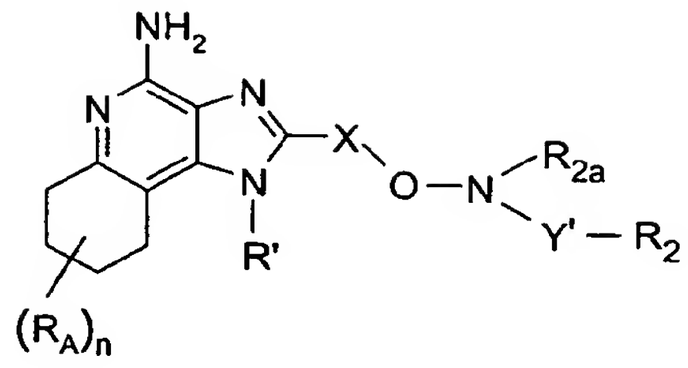
Despite important progress in the effort to find immunomodulating compounds, there is still a critical scientific and medical need for additional compounds that have an ability to modulate aspects of the immune response, by induction or inhibition of cytokine biosynthesis or other mechanisms.

SUMMARY

The present invention provides a new class of compounds that are useful in inducing cytokine biosynthesis in animals. Such compounds are of the following Formulas I and II:



I



II

wherein: R', R'", R_A, R_2, R_{2a}, n, X, and Y' are as defined below.

The compounds of Formulas I and II are useful as immune response modifiers (IRMs) due to their ability to induce cytokine biosynthesis (e.g., induce the biosynthesis or production of one or more cytokines) and otherwise modulate the immune response when administered to animals. This makes the compounds useful in the treatment of a variety of conditions, such as viral diseases and neoplastic diseases, that are responsive to such changes in the immune response.

In another aspect, the present invention provides pharmaceutical compositions containing the immune response modifier compounds, and methods of inducing cytokine biosynthesis in an animal, treating a viral disease in an animal, and treating a neoplastic disease in an animal, by administering an effective amount of one or more compounds of Formula I (or Ia described below) and/or Formula II (or IIa described below) and/or pharmaceutically acceptable salts thereof to the animal.

In another aspect, the invention provides methods of synthesizing compounds of Formulas I and II and intermediates useful in the synthesis of these compounds.

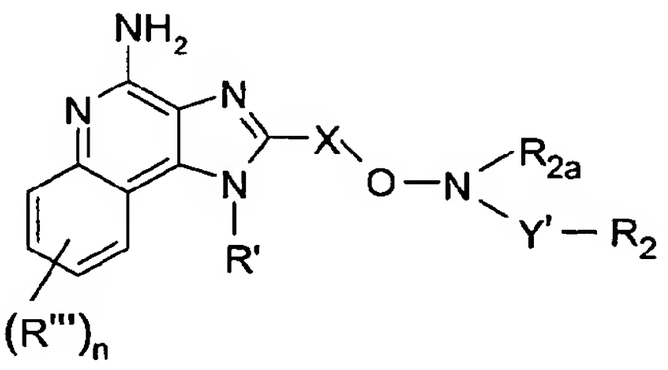
As used herein, "a," "an," "the," "at least one," and "one or more" are used interchangeably.

The terms "comprising" and variations thereof do not have a limiting meaning where these terms appear in the description and claims.

The above summary of the present invention is not intended to describe each disclosed embodiment or every implementation of the present invention. The description that follows more particularly exemplifies illustrative embodiments. Guidance is also provided herein through lists of examples, which can be used in various combinations. In each instance, the recited list serves only as a representative group and should not be interpreted as an exclusive list.

DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS OF THE INVENTION

In one aspect, the present invention provides compounds of the following Formula I:



I

wherein:

X is C_{1-10} alkylene or C_{2-10} alkenylene;

Y' is selected from the group consisting of:

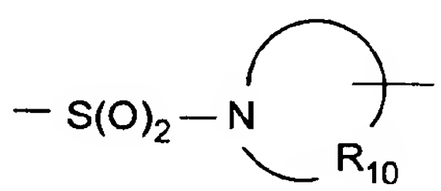
a bond,

-C(O)-,

-C(S)-,

$-S(O)_2-$,

$-S(O)_2-N(R_8)-$,



,

-C(O)-O-,

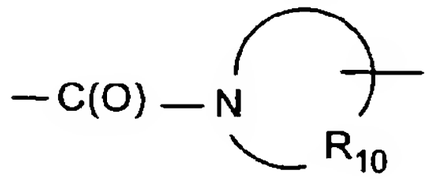
$-C(O)-N(R_8)-$,

-C(S)-$N(R_8)$-,

$-C(O)-N(R_8)-S(O)_2-$,

$-C(O)-N(R_8)-C(O)-$,

-C(S)-$N(R_8)$-C(O)-,



,

-C(O)-C(O)-,

-C(O)-C(O)-O-, and

-C(=NH)-N(R_8)-;

R_2 and R_{2a} are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxyl,

alkyl,

haloalkyl,

hydroxyalkyl,

alkoxy,

dialkylamino,

-$S(O)_{0-2}$-alkyl,

-$S(O)_{0-2}$-aryl,

-NH-$S(O)_2$-alkyl,

-NH-$S(O)_2$-aryl,

haloalkoxy,

halogen,

nitrile,

nitro,

aryl,

heteroaryl,

heterocyclyl,

aryloxy,

arylalkyleneoxy,

-C(O)-O-alkyl,

-C(O)-N(R_8)$_2$,

-N(R_8)-C(O)-alkyl,

-O-(CO)-alkyl, and

-C(O)-alkyl;

each R_8 is independently selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

R_{10} is C_{3-8} alkylene;

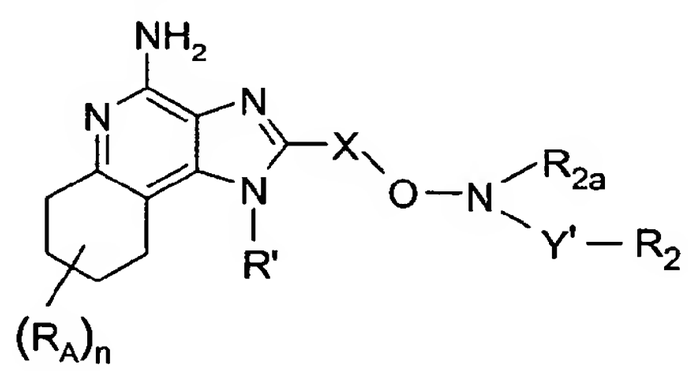
n is 0 to 4;

each R'" is a non-interfering substituent; and

R' is hydrogen or a non-interfering substituent;

or a pharmaceutically acceptable salt thereof.

The present invention also provides compounds of the following Formula II:



II

wherein:

X is C_{1-10} alkylene or C_{2-10} alkenylene;

Y' is selected from the group consisting of:

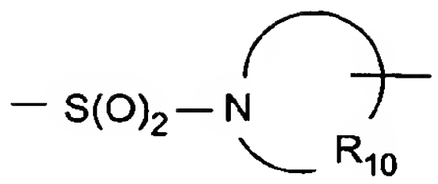
a bond,

-C(O)-,

-C(S)-,

-S(O)$_2$-,

-S(O)$_2$-N(R_8)-,



,

-C(O)-O-,

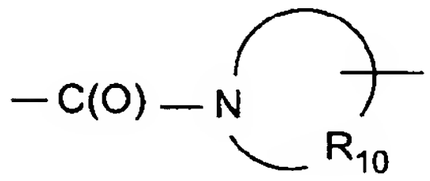
-C(O)-N(R_8)-,

-C(S)-N(R_8)-,

-C(O)-N(R_8)-S(O)$_2$-,

-C(O)-N(R_8)-C(O)-,

-C(S)-N(R_8)-C(O)-,



,

-C(O)-C(O)-,

-C(O)-C(O)-O-, and

-C(=NH)-N(R_8)-;

R_2 and R_{2a} are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxyl,

alkyl,

haloalkyl,

hydroxyalkyl,

alkoxy,
dialkylamino,
-S(O)$_{0-2}$-alkyl,
-S(O)$_{0-2}$-aryl,
-NH-S(O)$_2$-alkyl,
-NH-S(O)$_2$-aryl,
haloalkoxy,
halogen,
nitrile,
nitro,
aryl,
heteroaryl,
heterocyclyl,
aryloxy,
arylalkyleneoxy;
-C(O)-O-alkyl,
-C(O)-N(R_8)$_2$,
-N(R_8)-C(O)-alkyl,
-O-(CO)-alkyl, and
-C(O)-alkyl;

each R_8 is independently selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

R_{10} is C_{3-8} alkylene;

n is 0 to 4;

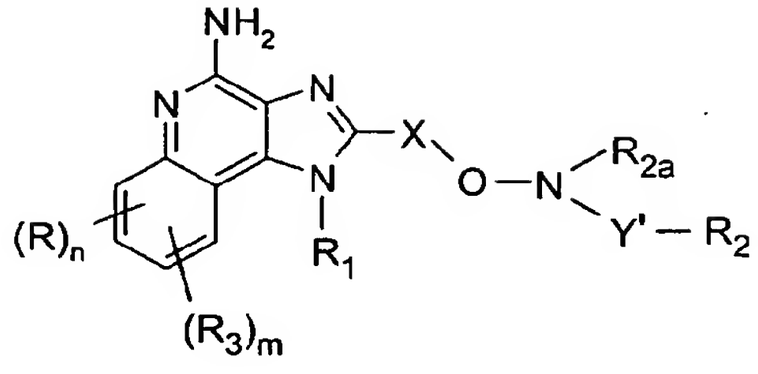
each R_A is independently selected from the group consisting of halogen, hydroxy, alkyl, alkenyl, haloalkyl, alkoxy, alkylthio, and –N(R_9)$_2$;

each R_9 is independently selected from the group consisting of hydrogen and alkyl; and

R' is hydrogen or a non-interfering substituent;

or a pharmaceutically acceptable salt thereof.

In one embodiment, the present invention provides compounds of the Formula Ia:



Ia

wherein:

X is C_{1-10} alkylene or C_{2-10} alkenylene;

Y' is selected from the group consisting of:

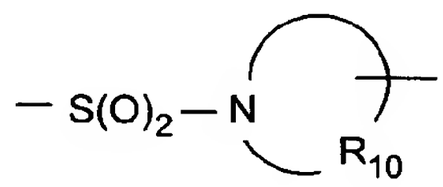
a bond,

-C(O)-,

-C(S)-,

-$S(O)_2$-,

-$S(O)_2$-$N(R_8)$-,



,

-C(O)-O-,

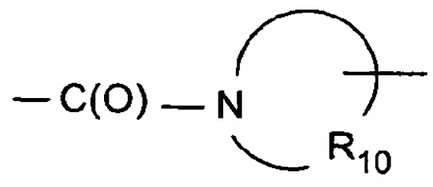
-$C(O)$-$N(R_8)$-,

-$C(S)$-$N(R_8)$-,

-$C(O)$-$N(R_8)$-$S(O)_2$-,

-$C(O)$-$N(R_8)$-C(O)-,

-$C(S)$-$N(R_8)$-C(O)-,



,

-C(O)-C(O)-,

-C(O)-C(O)-O-, and

-$C(=NH)$-$N(R_8)$-;

R_2 and R_{2a} are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxyl,

alkyl,

haloalkyl,

hydroxyalkyl,

alkoxy,

dialkylamino,

$-S(O)_{0-2}$-alkyl,

$-S(O)_{0-2}$-aryl,

$-NH-S(O)_2$-alkyl,

$-NH-S(O)_2$-aryl,

haloalkoxy,

halogen,

nitrile,

nitro,

aryl,

heteroaryl,

heterocyclyl,

aryloxy,

arylalkyleneoxy,

-C(O)-O-alkyl,

$-C(O)-N(R_8)_2$,

-N(R_8)-C(O)-alkyl,

-O-(CO)-alkyl, and

-C(O)-alkyl;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

-N(R_9)$_2$;

R_1 is selected from the group consisting of:

-R_4,

-X'-R_4,

-X'-Y-R_4,

-X'-Y-X'-Y-R_4,

-X'-R_5,

-X"-O-NH-Y'-R_1', and

-X"-O-N=C(R_1')(R_1");

R_3 is selected from the group consisting of:

-Z-R_4,

-Z-X'-R_4,

-Z-X'-Y-R_4,

-Z-X'-Y-X'-Y-R_4, and

-Z-X'-R_5;

n is 0 to 4;

m is 0 or 1; with the proviso that when m is 1, then n is 0 or 1;

each X' is independently selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene,

alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

X" is $-CH(R_{13})$alkylene or $-CH(R_{13})$alkenylene;

each Y is independently selected from the group consisting of:

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

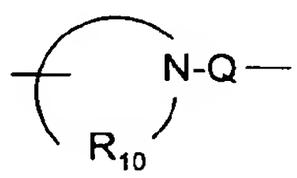
-O-C(O)-O-,

$-N(R_8)-Q-$,

$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

$-C(R_6)-N(OR_9)-$,



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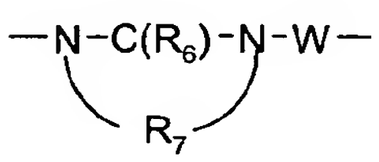

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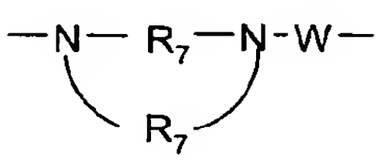

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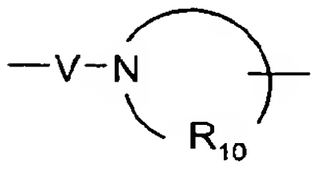
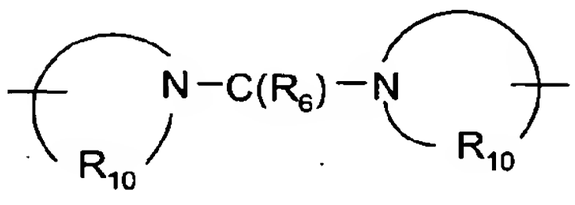


, and



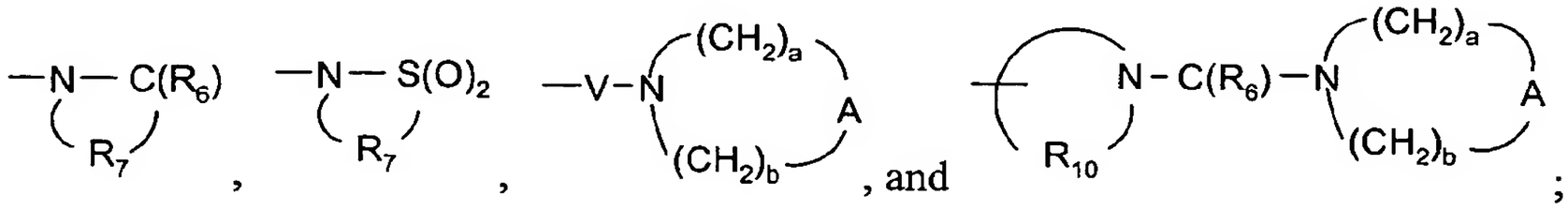
;

Z is a bond or -O-;

each R_4 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl,

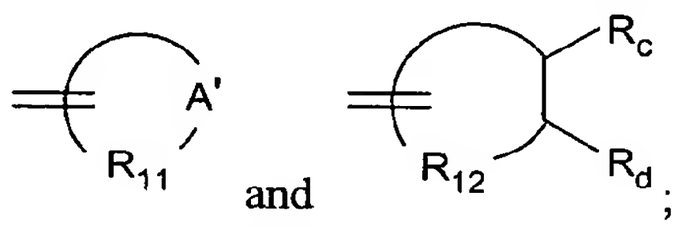
heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

each R_5 is independently selected from the group consisting of



;

R_1', and R_1'' are independently the same as R_2, or R_1' and R_1'' can join together to form a ring system selected from the group consisting of



;

R_c and R_d are independently selected from the group consisting of hydrogen, halogen, hydroxy, alkyl, alkenyl, aryl, haloalkyl, alkoxy, alkylthio, and $-N(R_9)_2$; or R_c and R_d can join to form a fused aryl ring or fused 5-10 membered heteroaryl ring containing one to four hetero atoms;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

each R_8 is independently selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

each R_9 is independently selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

R_{11} is C_{3-9} alkylene or C_{3-9} alkenylene, optionally interrupted by one hetero atom;

R_{12} is C_{2-7} alkylene or C_{2-7} alkenylene, optionally interrupted by one hetero atom;

R_{13} is selected from the group consisting of hydrogen and alkyl which may be optionally interrupted by one or more -O- groups;

A is selected from the group consisting of $-CH_2-$, -O-, -C(O)-, $-S(O)_{0-2}-$, and $-N(R_4)-$;

A' is selected from the group consisting of -O-, $-S(O)_{0-2}-$, $-N(-Q-R_4)-$. and $-CH_2-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

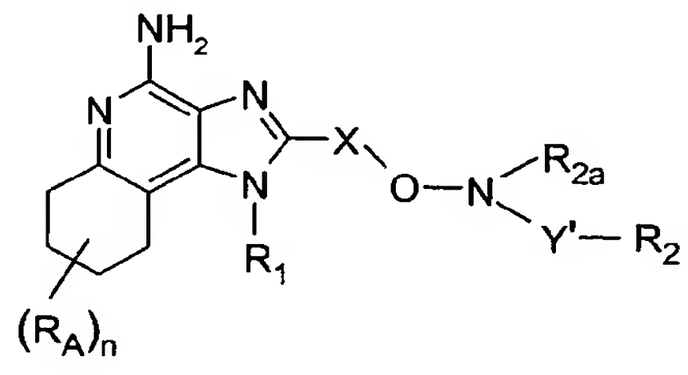
V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$; and

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

or a pharmaceutically acceptable salt thereof.

In another embodiment, the present invention provides compounds of the Formula IIa:



IIa

wherein:

X is C_{1-10} alkylene or C_{2-10} alkenylene;

Y' is selected from the group consisting of:

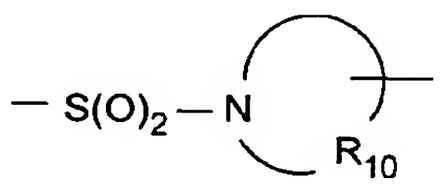
a bond,

-C(O)-,

-C(S)-,

$-S(O)_2-$,

$-S(O)_2-N(R_8)-$,



,

-C(O)-O-,

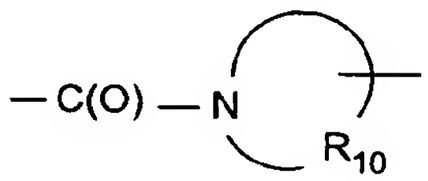
$-C(O)-N(R_8)-$,

$-C(S)-N(R_8)-$,

-C(O)-N(R_8)-S(O)$_2$-,

-C(O)-N(R_8)-C(O)-,

-C(S)-N(R_8)-C(O)-,



,

-C(O)-C(O)-,

-C(O)-C(O)-O-, and

-C(=NH)-N(R_8)-;

R_2 and R_{2a} are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxyl,

alkyl,

haloalkyl,

hydroxyalkyl,

alkoxy,

dialkylamino,

-S(O)$_{0-2}$-alkyl,

-S(O)$_{0-2}$-aryl,

-NH-S(O)$_2$-alkyl,

-NH-S(O)$_2$-aryl,

haloalkoxy,
halogen,
nitrile,
nitro,
aryl,
heteroaryl,
heterocyclyl,
aryloxy,
arylalkyleneoxy;
-C(O)-O-alkyl,
-C(O)-N(R_8)$_2$,
-N(R_8)-C(O)-alkyl,
-O-(CO)-alkyl, and
-C(O)-alkyl;

R_A is selected from the group consisting of:
halogen,
hydroxy,
alkyl,
alkenyl,
haloalkyl,
alkoxy,
alkylthio, and
-N(R_9)$_2$;

n is 0 to 4;

R_1 is selected from the group consisting of:
-R_4,
-X'-R_4,
-X'-Y-R_4,
-X'-Y-X'-Y-R_4,
-X'-R_5,
-X"-O-NH-Y'-R_1', and

-X"-O-N=C(R_1')(R_1");

each X' is independently selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

X" is –CH(R_{13})alkylene or –CH(R_{13})alkenylene;

each Y is independently selected from the group consisting of:

-S(O)$_{0-2}$-,

-S(O)$_2$-N(R_8)-,

-C(R_6)-,

-C(R_6)-O-,

-O-C(R_6)-,

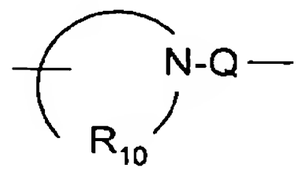
-O-C(O)-O-,

-N(R_8)-Q-,

-C(R_6)-N(R_8)-,

-O-C(R_6)-N(R_8)-,

-C(R_6)-N(OR_9)-,



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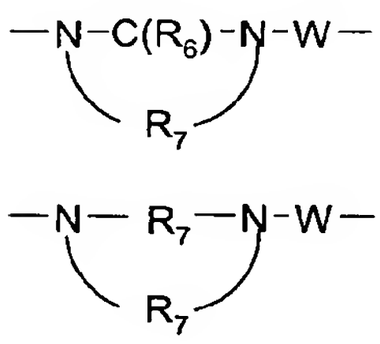

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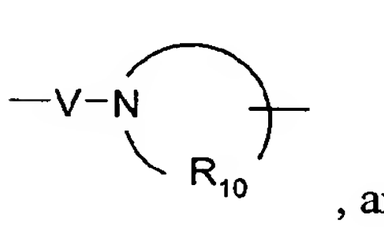

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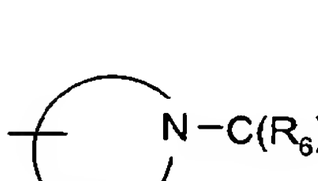


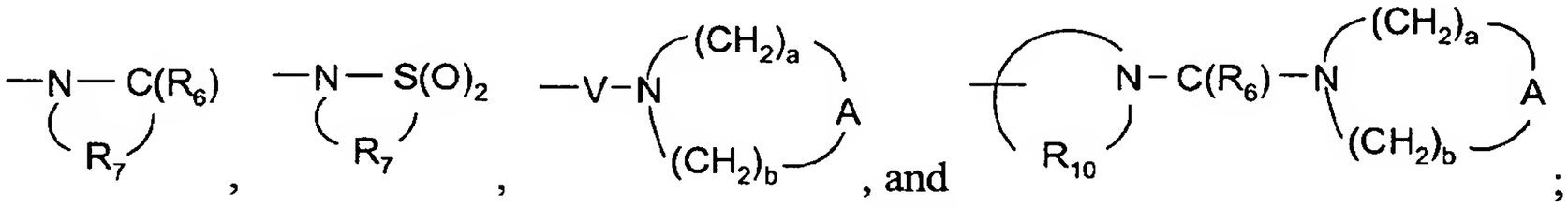
, and

;

each R_4 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl,

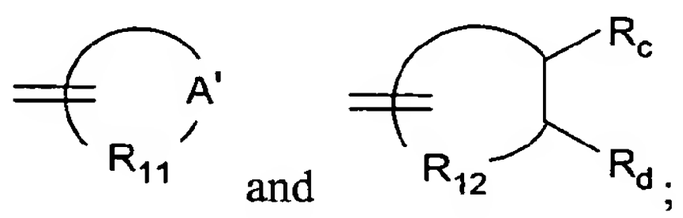
heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

each R_5 is independently selected from the group consisting of



;

R_1', and R_1'' are independently R_2, or R_1' and R_1'' can join together to form a ring system selected from the group consisting of



;

R_c and R_d are independently selected from the group consisting of hydrogen, halogen, hydroxy, alkyl, alkenyl, aryl, haloalkyl, alkoxy, alkylthio, and $-N(R_9)_2$; or R_c and R_d can join to form a fused aryl ring or fused 5-10 membered heteroaryl ring containing one to four hetero atoms;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

each R_8 is independently selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

each R_9 is independently selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

R_{11} is C_{3-9} alkylene or C_{3-9} alkenylene, optionally interrupted by one hetero atom;

R_{12} is C_{2-7} alkylene or C_{2-7} alkenylene, optionally interrupted by one hetero atom;

R_{13} is selected from the group consisting of hydrogen and alkyl which may be optionally interrupted by one or more -O- groups;

A is selected from the group consisting of $-CH_2-$, -O-, -C(O)-, $-S(O)_{0-2}-$, and $-N(R_4)-$;

A' is selected from the group consisting of -O-, $-S(O)_{0-2}-$, $-N(-Q-R_4)-$. and $-CH_2-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$; and

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

or a pharmaceutically acceptable salt thereof.

Herein, "non-interfering" means that the ability of the compound or salt to modulate the biosynthesis of one or more cytokines is not destroyed by the non-interfering substitutent. Illustrative non-interfering R' groups include those described above for R_1. Illustrative non-interfering R'" groups include those described above for R and R_3.

As used herein, the terms "alkyl," "alkenyl," "alkynyl" and the prefix "alk-" are inclusive of both straight chain and branched chain groups and of cyclic groups, i.e. cycloalkyl and cycloalkenyl. Unless otherwise specified, these groups contain from 1 to 20 carbon atoms, with alkenyl groups containing from 2 to 20 carbon atoms, and alkynyl groups containing from 2 to 20 carbon atoms. In some embodiments, these groups have a total of up to 10 carbon atoms, up to 8 carbon atoms, up to 6 carbon atoms, or up to 4 carbon atoms. Cyclic groups can be monocyclic or polycyclic and preferably have from 3 to 10 ring carbon atoms. Exemplary cyclic groups include cyclopropyl, cyclopropylmethyl, cyclopentyl, cyclohexyl, adamantyl, and substituted and unsubstituted bornyl, norbornyl, and norbornenyl.

Unless otherwise specified, "alkylene," "alkenylene," and "alkynylene" are the divalent forms of the "alkyl," "alkenyl," and "alkynyl" groups defined above. Likewise, "alkylenyl," "alkenylenyl," and "alkynylenyl" are the divalent forms of the "alkyl,"

"alkenyl," and "alkynyl" groups defined above. For example, an arylalkylenyl group comprises an alkylene moiety to which an aryl group is attached.

The term "haloalkyl" is inclusive of groups that are substituted by one or more halogen atoms, including perfluorinated groups. This is also true of other groups that include the prefix "halo-". Examples of suitable haloalkyl groups are chloromethyl, trifluoromethyl, and the like.

The term "aryl" as used herein includes carbocyclic aromatic rings or ring systems. Examples of aryl groups include phenyl, naphthyl, biphenyl, fluorenyl and indenyl.

The term "heteroatom" refers to the atoms O, S, or N.

The term "heteroaryl" includes aromatic rings or ring systems that contain at least one ring heteroatom (e.g., O, S, N). Suitable heteroaryl groups include furyl, thienyl, pyridyl, quinolinyl, isoquinolinyl, indolyl, isoindolyl, triazolyl, pyrrolyl, tetrazolyl, imidazolyl, pyrazolyl, oxazolyl, thiazolyl, benzofuranyl, benzothiophenyl, carbazolyl, benzoxazolyl, pyrimidinyl, benzimidazolyl, quinoxalinyl, benzothiazolyl, naphthyridinyl, isoxazolyl, isothiazolyl, purinyl, quinazolinyl, pyrazinyl, 1-oxidopyridyl, pyridazinyl, triazinyl, tetrazinyl, oxadiazolyl, thiadiazolyl, and so on.

The term "heterocyclyl" includes non-aromatic rings or ring systems that contain at least one ring heteroatom (e.g., O, S, N) and includes all of the fully saturated and partially unsaturated derivatives of the above mentioned heteroaryl groups. Exemplary heterocyclic groups include pyrrolidinyl, tetrahydrofuranyl, morpholinyl, thiomorpholinyl, piperidinyl, piperazinyl, thiazolidinyl, imidazolidinyl, isothiazolidinyl, tetrahydropyranyl, quinuclidinyl, homopiperidinyl, and the like.

The terms "arylene," "heteroarylene," and "heterocyclylene" are the divalent forms of the "aryl," "heteroaryl," and "heterocyclyl" groups defined above. Likewise, "arylenyl," "heteroarylenyl," and "heterocyclylenyl" are the divalent forms of the "aryl," "heteroaryl," and "heterocyclyl" groups defined above. For example, an alkylarylenyl group comprises an arylene moiety to which an alkyl group is attached.

In some embodiments of Formula I, R' is selected from the group consisting of:

$-R_4$,

$-X'-R_4$,

-X'-Y-R_4,

-X'-Y-X'-Y-R_4,

-X'-R_5,

-X''-O-NH-Y'-R_1', and

-X''-O-N=C(R_1')(R_1'');

wherein X', X'', Y, Y', R_1', R_1'', R_4, and R_5, are as defined above.

In some embodiments of Formula I, R''' is R or R_3 when n is 1, R or one R and one R_3 when n is 2, or R when n is 3 to 4;

wherein:

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

-N(R_9)$_2$;

R_3 is selected from the group consisting of:

-Z-R_4,

-Z-X'-R_4,

-Z-X'-Y-R_4,

-Z-X'-Y-X'-Y-R_4, and

-Z-X'-R_5;

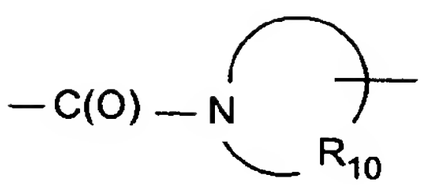
n is 0 to 4;

Z is a bond or -O-; and

X', Y, R_4, R_5, and R_9 are as defined above.

In some embodiments of Formulas Ia and IIa, X is C_{1-4} alkylene.

In some embodiments of Formulas Ia and IIa, Y' is selected from the group consisting of a bond, -C(O)-, -C(O)-O-, -S(O)$_2$-, -S(O)$_2$-N(R_8)-, -C(O)-N(R_8)-, -C(O)-N(R_8)-C(O)-, and



In some embodiments of Formulas Ia and IIa, R_2 and R_{2a} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, aryl, heteroaryl, wherein the alkyl, alkenyl, aryl, and heteroaryl are each optionally substituted with one or more substitutents selected from the group consisting of $C_{1\text{-}10}$ alkyl, aryl, heteroaryl, $C_{1\text{-}10}$ alkoxy, -O-C(O)-$C_{1\text{-}10}$ alkyl, -C(O)-O-$C_{1\text{-}10}$ alkyl, halogen, and nitrile.

In some embodiments of Formulas Ia and IIa, R_{2a} is hydrogen.

In some embodiments of Formulas Ia and IIa, R_2 alkyl or substituted alkyl, and R_{2a} is hydrogen.

In some embodiments of Formulas Ia and IIa, R_2 is alkenyl or substituted alkenyl, and R_{2a} is hydrogen.

In some embodiments of Formulas Ia and IIa, R_2 is aryl, arylalkylenyl, substituted aryl, or substituted arylalkylenyl, and R_{2a} is hydrogen.

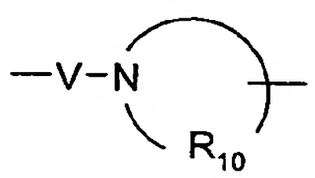
In some embodiments of Formulas Ia and IIa, R_2 is heteroaryl, heteroarylalkylenyl, substituted heteroaryl, or substituted heteroarylalkylenyl, and R_{2a} is hydrogen.

In some embodiments of Formulas Ia and IIa, R_2 is heterocyclyl, heterocyclylalkylenyl, substituted heterocyclyl, or substituted heterocyclylalkylenyl, and R_{2a} is hydrogen.

In some embodiments of Formulas Ia and IIa, R_2 is selected from the group consisting of methyl, (ethoxycarbonyl)methyl, ethyl, cyclopropyl, cyclopropylmethyl, 2-(ethoxycarbonyl)cyclopropylmethyl, propyl, butyl, 2-methylpropyl, *tert*-butyl, 3-methylbutyl, 2,2-dimethylpropyl, cyclopentyl, 2-cyclopentylethyl, furyl, fur-3-ylmethyl, furfuryl, furfurylmethyl, cyclohexyl, tetrahydrofuranyl, tetrahydrofuran-3-ylmethyl, 2-(methylthio)ethyl, 2-(methylthio)propyl, phenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2,6-dimethoxyphenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-cyanophenyl, 3-cyanophenyl, 4-cyanophenyl, 4-(dimethylamino)phenyl, 3-hydroxy-4-methoxyphenyl, 4-acetamidophenyl, 4-(methoxycarbonyl)phenyl, 4-(trifluoromethyl)phenyl, biphenyl, benzyl, 2-methylbenzyl, 3-methylbenzyl, 4-methylbenzyl, 2-fluorobenzyl, 3-fluorobenzyl, 4-fluorobenzyl, 2-

chlorobenzyl, 3-chlorobenzyl, 4-chlorobenzyl, 2-cyanobenzyl, 3-cyanobenzyl, 4-cyanobenzyl, 2-methoxybenzyl, 3-methoxybenzyl, 4-methoxybenzyl, 4-dimethylaminobenzyl, 3-hydroxy-4-methoxybenzyl, 4-acetamidobenzyl, 4-(methoxycarbonyl)benzyl, 4-(trifluoromethyl)benzyl, 1-phenylethyl, 2-phenylethyl, 2-phenylpropyl, 3-phenylpropyl, 2-phenylethenyl, phenoxymethyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyridylmethyl, 3-pyridylmethyl, 4-pyridylmethy, 1-methylpyrrol-2-yl, 1-methylpyrrol-2-ylmethyl, 1-methylimidazol-2-yl, 1-methylimidazol-2-ylmethyl, 1-methylimidazol-4-yl, 1-methylimidazol-4-ylmethyl, 3-cyclohexen-1-yl, 3-cyclohexen-1-ylmethyl, 3,4-dihydro-2*H*-pyran-2-yl, 3,4-dihydro-2*H*-pyran-2-ylmethyl, 1-methylpiperidin-4-yl, 1-acetylpiperidin-4-yl, 1-benzylpiperidin-4-yl, 2-thienyl, 3-thienyl, thien-2-ylmethyl, thiazol-2-yl, thiazol-2-ylmethyl, 5-isoxazolyl, 5-isoxazolylmethyl, quinolin-2-yl, quinolin-2-ylmethyl, and pyrrolidinyl; and R_{2a} is hydrogen.

In some embodiments of Formulas Ia and IIa, R_1 is selected from the group consisting of alkyl, arylalkylenyl, aryloxyalkylenyl, hydroxyalkyl, alkylsulfonylalkylenyl, -X'-Y-R_4, and -X'-R_5; wherein X' is alkylene; Y is -N(R_8)-C(O)-, -N(R_8)-S(O)$_2$-, -N(R_8)-S(O)$_2$-N(R_8)-, -N(R_8)-C(O)-N(R_8)-, -N(R_8)-C(O)-N(R_8)-C(O)-,



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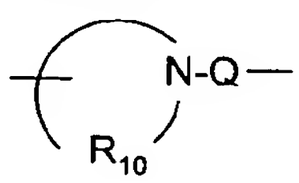
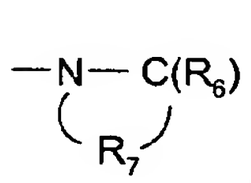


; R_4 is hydrogen, alkyl, alkenyl, aryl, or heteroaryl; and R_5 is



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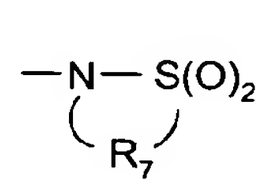

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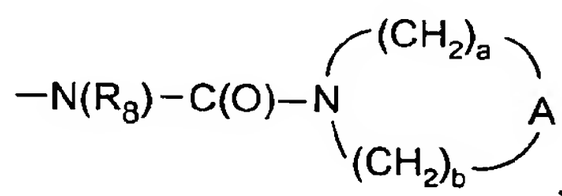
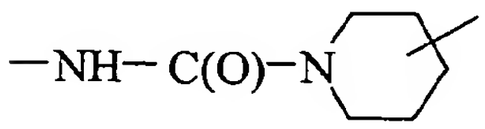


. In certain embodiments, R_1 is 2-methylpropyl or –X'-Y-R_4; X' is ethylene, propylene, or butylene; Y is -NH-C(O)-, -NH-S(O)$_2$-, -NH-S(O)$_2$-N(R_8)-, -NH-C(O)-N(R_8)-, -NH-C(O)-NH-C(O)-, or



; and R_8 is hydrogen or methyl.

In some embodiments of Formula Ia, n and m are 0.

In some embodiments of Formula IIa, n is 0.

The invention is inclusive of the compounds described herein in any of their pharmaceutically acceptable forms, including isomers (e.g., diastereomers and enantiomers), salts, solvates, polymorphs, and the like. In particular, if a compound is

optically active, the invention specifically includes each of the compound's enantiomers as well as racemic mixtures of the enantiomers.

Preparation of the Compounds

Compounds of the invention can be prepared according to Reaction Scheme I where R, R_1, X, and n are as defined above, Hal is chloro, bromo, or iodo, and R_2' and R_2" are the same as R_1' and R_1" as defined above. In step (1) of Reaction Scheme I, a quinoline-3,4-diamine of Formula V is reacted with a carboxylic acid or an equivalent thereof to provide a 1*H*-imidazo[4,5-*c*]quinoline of Formula VI. Suitable equivalents to a carboxylic acid include orthoesters, and 1,1-dialkoxyalkyl alkanoates. The carboxylic acid or equivalent is selected such that it will provide the desired –X-Hal substituent in a compound of Formula VI. For example, Hal-X-CO_2H or Hal-X-C(O-alkyl)$_3$ will provide a compound with the desired
–X-Hal substitutent at the 2-position. The reaction can be run in the absence of solvent or in an inert solvent such as toluene. The reaction is run with sufficient heating to drive off any alcohol or water formed as a byproduct of the reaction. Optionally a catalyst such as pyridine hydrochloride can be included.

Alternatively, step (1) can be carried out by (i) reacting a compound of Formula V with an acyl halide of formula Hal-X-C(O)Cl or Hal-X-C(O)Br and then (ii) cyclizing. In part (i) the acyl halide is added to a solution of a compound of Formula V in an inert solvent such as acetonitrile, pyridine or dichloromethane. The reaction can be carried out at ambient temperature. A catalyst such as pyridine hydrochloride can be included. In part (ii) the product of part (i) is heated in pyridine. The two steps can be combined into a single step when the reaction is run in such solvents as pyridine, dichloromethane, or dichloroethane.

Many compounds of Formula V are known and can be readily prepared using known synthetic routes; see for example, U.S. Patent Nos. 4,689,338 (Gerster), 4,929,624 (Gerster et al.), 5,268,376 (Gerster), 5,389,640 (Gerster et al.), 6,331,539 (Crooks et al.), 6,451,810 (Coleman et al.), 6,541,485 (Crooks et al.) and PCT Publication Nos.WO 02/46188, WO 02/46189, WO 02/46190, WO 02/46191, and WO 02/46192.

In step (2) of Reaction Scheme I a 1*H*-imidazo[4,5-*c*]quinoline of Formula VI is oxidized to provide an N-oxide of Formula VII using a conventional oxidizing agent that is capable of forming N-oxides. The reaction can be carried out by treating a solution of a compound of Formula VI in a suitable solvent such as chloroform or dichloromethane with 3-chloroperoxybenzoic acid at ambient temperature.

In step (3) of Reaction Scheme I an N-oxide of Formula VII is aminated to provide a 1*H*-imidazo[4,5-*c*]quinoline-4-amine of Formula VIII. The reaction is carried out in two parts. In part (i) a compound of Formula VII is reacted with an acylating agent. Suitable acylating agents include alkyl- or arylsulfonyl chorides (e.g., benzenesulfonyl choride, methanesulfonyl choride, or *p*-toluenesulfonyl chloride). In part (ii) the product of part (i) is reacted with an excess of an aminating agent. Suitable aminating agents include ammonia (e.g. in the form of ammonium hydroxide) and ammonium salts (e.g., ammonium carbonate, ammonium bicarbonate, ammonium phosphate). The reaction can be carried out by dissolving a compound of Formula VII in a suitable solvent such as dichloromethane or chloroform, adding ammonium hydroxide to the solution, and then adding *p*-toluenesulfonyl chloride. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

In step (4) of Reaction Scheme I a 1*H*-imidazo[4,5-*c*]quinoline-4-amine of Formula VIII is treated with *N*-hydroxyphthalimide to provide an *N*-phthalimide-protected 1*H*-imidazo[4,5-*c*]quinolin-2-yl hydroxylamine of Formula IX. The reaction is conveniently carried out by adding a base, such as triethylamine, to a solution of *N*-hydroxyphthalimide in a suitable solvent such as *N,N*-dimethylformamide (DMF); and then adding the 1*H*-imidazo[4,5-*c*]quinoline-4-amine of Formula VIII in a suitable solvent (for example, DMF) to the resulting mixture. The reaction can be carried out at ambient temperature. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

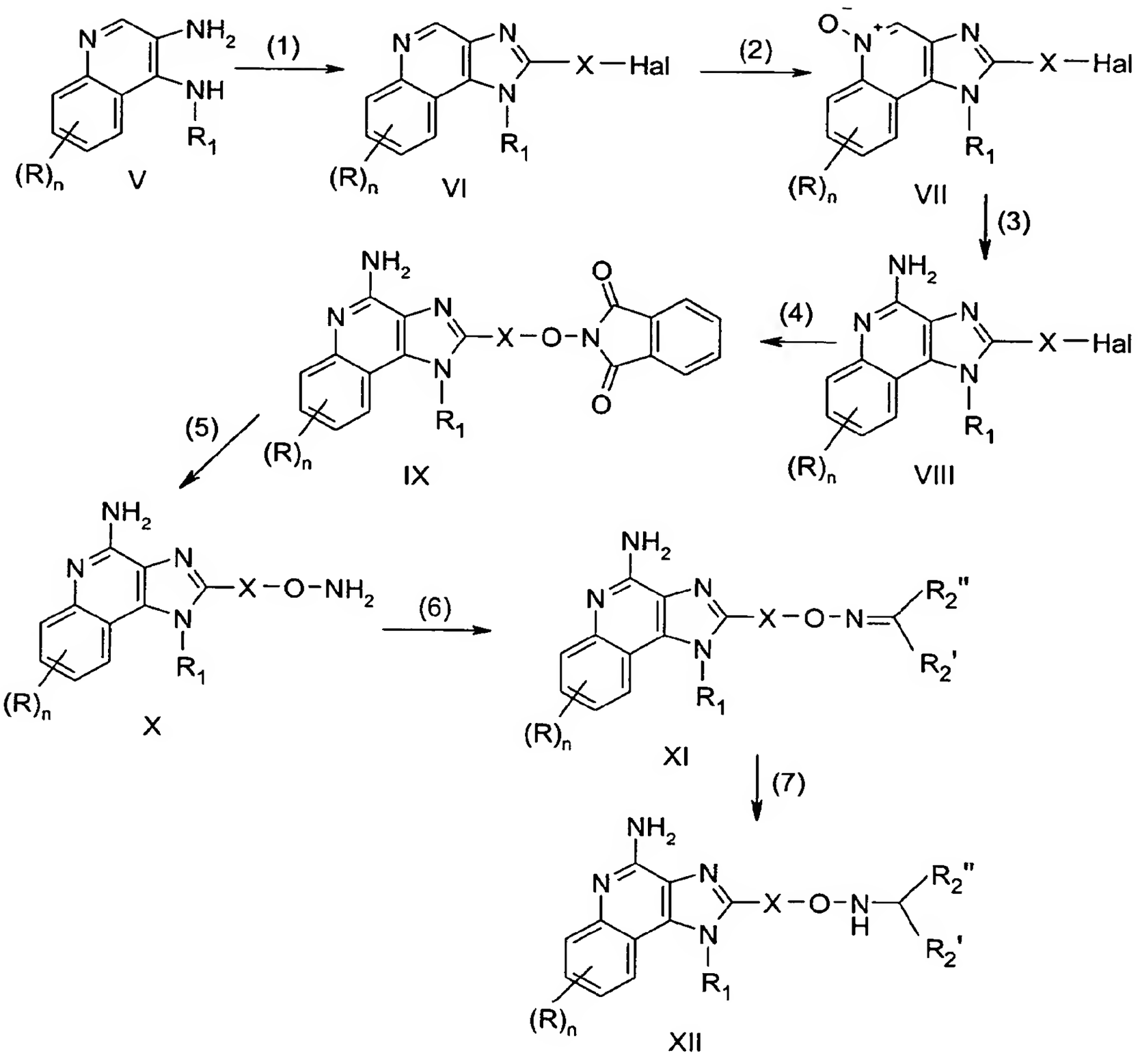
In step (5) of Reaction Scheme I an *N*-phthalimide-protected 1*H*-imidazo[4,5-*c*]quinolin-2-yl hydroxylamine of Formula IX is converted to a 1*H*-imidazo[4,5-*c*]quinolin-2-yl hydroxylamine of Formula X. Removal of the *N*-phthalimide protecting group is conveniently carried out by adding hydrazine to a suspension of an *N*-phthalimide-protected 1*H*-imidazo[4,5-*c*]quinolin-2-yl hydroxylamine of Formula IX in a

suitable solvent such as ethanol. The reaction can be carried out at ambient temperature. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

In step (6) of Reaction Scheme I a 1*H*-imidazo[4,5-*c*]quinolin-2-yl hydroxylamine of Formula X is reacted with an aldehyde or ketone of formula $R_2'C(O)R_2''$ to provide a 1*H*-imidazo[4,5-*c*]quinolin-2-yl oxime of Formula XI. Numerous aldehydes and ketones of formula $R_2'C(O)R_2''$ are commercially available; others can be readily prepared using known synthetic methods. The reaction can be conveniently carried out by adding the aldehyde or ketone of formula $R_2'C(O)R_2''$ to a 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula X in a suitable solvent such as methanol. The reaction can be carried out at ambient temperature. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

In step (7) of Reaction Scheme I a 1*H*-imidazo[4,5-*c*]quinolin-2-yl oxime of Formula XI is reduced to provide a 1*H*-imidazo[4,5-*c*]quinolin-2-yl hydroxylamine of Formula XII, which is a subgenus of Formulas I and Ia. The reduction is conveniently carried out by treating a 1*H*-imidazo[4,5-*c*]quinolin-2-yl oxime of Formula XI with excess sodium cyanoborohydride in a suitable solvent or solvent mixture such as methanol/acetic acid. The reaction can be carried out at ambient temperature. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Reaction Scheme I



Compounds of the invention can be prepared according to Reaction Scheme II where R, R_4, R_8, Q, X, X', Hal, and n are as defined above, Boc is *tert*-butoxycarbonyl, R_{5a} is R_5 wherein V is $-N(R_8)-C(R_6)-$, and R_2' and R_2'' are the same as R_1' and R_1'' as defined above. In step (1) of Reaction Scheme II a 1*H*-imidazo[4,5-*c*]quinolin-1-yl *tert*-butylcarbamate of Formula XIII is treated with *N*-hydroxyphthalimide to provide an *N*-phthalimide-protected 1*H*-imidazo[4,5-*c*]quinolin-2-yl hydroxylamine of Formula XIV. The reaction is conveniently carried out by adding a base, such as triethylamine, to *N*-hydroxyphthalimide dissolved in a suitable solvent such as DMF; and then adding the 1*H*-imidazo[4,5-*c*]quinolin-1-yl *tert*-butylcarbamate of Formula XIII in a suitable solvent (for

example, DMF) to the resulting mixture. The reaction can be carried out at ambient temperature. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods. Compounds of Formula XIII can be readily prepared using known synthetic routes; see for example, U.S. Patent No. 6,451,810 (Coleman et al.), and PCT Publication No. WO 02/46188.

In step (2) of Reaction Scheme II an *N*-phthalimide-protected 1*H*-imidazo[4,5-*c*]quinolin-2-yl hydroxylamine of Formula XIV is converted to a 1*H*-imidazo[4,5-*c*]quinolin-2-yl hydroxylamine of Formula XV. Removal of the *N*-phthalimide protecting group is conveniently carried out by adding hydrazine to a suspension of an *N*-phthalimide-protected 1*H*-imidazo[4,5-*c*]quinolin-2-yl hydroxylamine of Formula XIV in a suitable solvent such as ethanol. The reaction can be carried out at ambient temperature. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

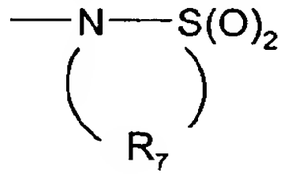
In step (3) of Reaction Scheme II a 1*H*-imidazo[4,5-*c*]quinolin-2-yl hydroxylamine of Formula XV is reacted with an aldehyde or ketone of formula $R_2'C(O)R_2''$ to provide a 1*H*-imidazo[4,5-*c*]quinolin-2-yl oxime of Formula XVI. Numerous aldehydes and ketones of formula $R_2'C(O)R_2''$ are commercially available; others can be readily prepared using known synthetic methods. The reaction can be conveniently carried out by adding the aldehyde or ketone of formula $R_2'C(O)R_2''$ to a solution of the 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula XV in a suitable solvent such as methanol. The reaction can be carried out at ambient temperature. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

In step (4) of Reaction Scheme II a 1*H*-imidazo[4,5-*c*]quinolin-2-yl oxime of Formula XVI is deprotected to provide an amino group at the 1-position of a 1*H*-imidazo[4,5-*c*]quinolin-2-yl oxime of Formula XVII. The reaction can be conveniently carried out by dissolving a compound of Formula XVI in a mixture of trifluoroacetic acid and a suitable solvent such as dichloromethane. The reaction can be carried out at ambient temperature. The product or a pharmaceutically acceptable salt thereof, including the trifluoroacetate salt, can be isolated using conventional methods.

In steps (5) and (5a) of Reaction Scheme II a 1*H*-imidazo[4,5-*c*]quinolin-2-yl oxime of Formula XVII is converted to a 1*H*-imidazo[4,5-*c*]quinolin-2-yl oxime of

Formula XVIII or XIX, using conventional methods. For example, sulfonamides of Formula XVIII (Q is
$-S(O)_2-$) can be prepared by reacting a compound of Formula XVII with a sulfonyl chloride of formula $R_4S(O)_2Cl$. The reaction can be carried out at ambient temperature in an inert solvent such as chloroform or dichloromethane by adding the sulfonyl chloride to a compound of Formula XVII in the presence of a base such as *N*,*N*-diisopropylethylamine, triethylamine, or pyridine. Sulfamides of Formula XVIII (Q is, for example, $-S(O)_2-N(R_8)-$) can be prepared by reacting a compound of Formula XVII with a sulfamoyl chloride of formula $R_4(R_8)NS(O)_2Cl$ or by reacting a compound of Formula XVII with sulfuryl chloride to generate a sulfamoyl chloride in situ, and then reacting the resulting sulfamoyl chloride with an amine of formula $HN(R_8)R_4$. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods. Some sulfamoyl chlorides of formula $R_4(R_8)NS(O)_2Cl$ and many sulfonyl chlorides of formula $R_4S(O)_2Cl$ and amines of formula $HN(R_8)R_4$ are commercially available; others can be prepared using known synthetic methods.

In another example, using step (5a) of Reaction Scheme II, a 1*H*-imidazo[4,5-*c*]quinolin-2-yl oxime of Formula XVII is reacted with a chloroalkanesulfonyl chloride of formula $Cl-R_7-S(O)_2Cl$ to provide a compound of Formula XIX, wherein R_{5a} is a ring having the structure

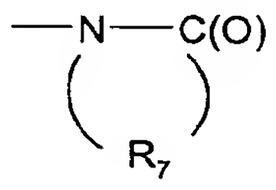


The reaction is preferably carried out by adding the chloroalkanesulfonyl chloride to a solution of a compound of Formula XVII in a suitable solvent such as dichloromethane in the presence of a base such as triethylamine. The intermediate chloroalkanesulfonamide may optionally be isolated before treatment with a stronger base such as 1,8-diazabicyclo[5.4.0]undecene-7 (DBU) at ambient temperature. If the intermediate chloroalkanesulfonamide is isolated, the reaction with DBU can be carried out in a suitable solvent such as DMF. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Amides of Formulas XVIII (Q is, for example, -C(O)-) and XIX can be prepared from 1*H*-imidazo[4,5-*c*]quinolin-2-yl oxime of Formula XVII using conventional methods.

For example, a compound of Formula XVII can be reacted with an acid chloride of formula $R_4C(O)Cl$ to provide a compound of Formula XVIII. The reaction can be carried out by adding the acid chloride to a solution of a compound of Formula XVII in a suitable solvent such as chloroform, optionally in the presence of a base such as *N*,*N*-diisopropylethylamine, triethylamine, or pyridine, at ambient temperature. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

In another example shown in step (5a), a 1*H*-imidazo[4,5-*c*]quinolin-2-yl oxime of Formula XVII is reacted with a chloroalkanoyl chloride compound of formula $Cl\text{-}R_7\text{-}C(O)Cl$ to provide a compound of Formula XIX, wherein R_{5a} is a ring having the structure



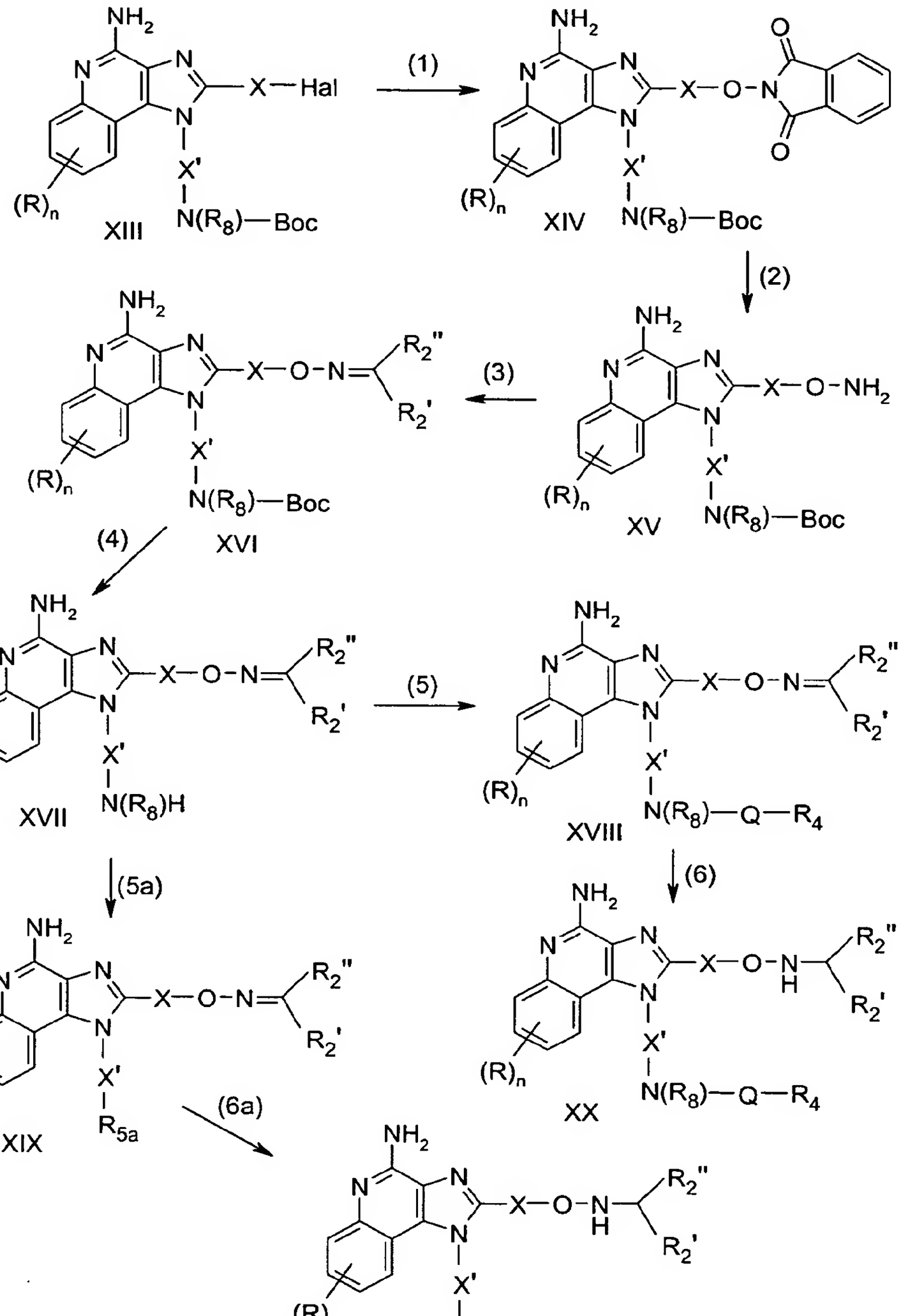
.

The reaction is preferably carried out by adding the chloroalkanoyl chloride compound to a compound of Formula XVII in a suitable solvent such as dichloromethane in the presence of a base such as *N*,*N*-diisopropylethylamine. The intermediate chloroalkanamide may optionally be isolated before treatment with a stronger base such as 1,8-diazabicyclo[5.4.0]undecene-7 (DBU) at ambient temperature. If the intermediate chloroalkanamide is isolated, the reaction with DBU can be carried out in a suitable solvent such as DMF. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Ureas and thioureas of Formula XVIII (Q is, for example, $-C(O)\text{-}N(R_8)\text{-}$ or $-C(S)\text{-}N(R_8)\text{-}$) and XIX can be prepared from 1*H*-imidazo[4,5-*c*]quinolin-2-yl oximes of Formula XVII using conventional methods. For example, a compound of Formula XVII can be reacted with an isocyanate of formula $R_4N{=}C{=}O$. The reaction can be carried out by adding the isocyanate to a solution of a compound of Formula XVII in a suitable solvent such as chloroform, optionally in the presence of a base such as *N*,*N*-diisopropylethylamine, or triethylamine, at ambient temperature. Alternatively, a compound of Formula XVII can be reacted with, for example, a thioisocyanate of formula $R_4N{=}C{=}S$, a sulfonyl isocyanate of formula $R_4S(O)_2N{=}C{=}O$ or a carbamoyl chloride of formula $R_4NC(O)Cl$. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

In steps (6) and (6a) of Reaction Scheme II a 1*H*-imidazo[4,5-*c*]quinolin-2-yl oxime of Formula XVIII or Formula XIX is reduced to provide a 1*H*-imidazo[4,5-*c*]quinolin-2-yl hydroxylamine of Formula XX or Formula XXI, each of which is a subgenus of Formulas I and Ia. The reduction is conveniently carried out by treating a 1*H*-imidazo[4,5-*c*]quinolin-2-yl oxime of Formula XVIII or Formula XIX with excess sodium cyanoborohydride in a suitable solvent or solvent mixture such as methanol/acetic acid. The reaction can be carried out at ambient temperature. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Reaction Scheme II



Compounds of the invention can be prepared according to Reaction Scheme III where n is as defined above; each R_B is independently selected from the group consisting of hydroxyl, alkyl, alkoxy, $-N(R_9)_2$; X_c is C_{1-10} alkylene; P is a removable protecting group,

such as an alkanoyloxy group (e.g., acetoxy) or an aroyloxy group (e.g., benzoyloxy); R_2' and R_2" are the same as R_1' and R_1" as defined above; and R_{1c} is a subset of R_1 as defined above, which does not include those groups that one skilled in the art would recognize as being susceptible to reduction in step (5). These groups include, for example, alkenyl, alkynyl, and aryl groups, and groups bearing nitro and –S- substitutents. In step (1) of Reaction Scheme III a quinoline-3,4-diamine of Formula Va is reacted with a carboxylic acid of the formula, HO-X-CO_2H, with a trialkyl ortho ester of the formula, HO-X-C(O-C_{1-4} alkyl)$_3$, or with a combination thereof (wherein "alkyl" is a straight or branched chain) to provide a 1*H*-imidazo[4,5-*c*]quinolin-2-yl alcohol of Formula XXII. The reaction is run with sufficient heating to drive off any alcohol or water formed as a byproduct of the reaction. Optionally a catalyst such as pyridine hydrochloride can be included.

In step (2) of Reaction Scheme III the hydroxyl group of a 1*H*-imidazo[4,5-*c*]quinoline of Formula XXII is protected with a removable protecting group such as an alkanoyloxy group (e.g., acetoxy) or aroyloxy group (e.g., benzoyloxy) to provide a 1*H*-imidazo[4,5-*c*]quinoline of Formula XXIII. Suitable protecting groups and reactions for their placement and removal are well known to those skilled in the art. See, for example, U.S. Patent No. 4,689,338 (Gerster), Examples 115 and 120.

In step (3) of Reaction Scheme III a 1*H*-imidazo[4,5-*c*]quinoline of Formula XXIII is oxidized to provide an N-oxide of Formula XXIV using a conventional oxidizing agent that is capable of forming N-oxides. The reaction can be carried out by treating a solution of a compound of Formula XXIII in a suitable solvent such as chloroform or dichloromethane with 3-chloroperoxybenzoic acid at ambient temperature.

In step (4) of Reaction Scheme III an N-oxide of Formula XXIV is aminated and the protecting group removed to provide a 1*H*-imidazo[4,5-*c*]quinoline-4-amine of Formula XXV. The amination reaction is carried out in two parts. In part (i) a compound of Formula XXIV is reacted with an acylating agent. Suitable acylating agents include alkyl- or arylsulfonyl chorides (e.g., benzenesulfonyl choride, methanesulfonyl choride, or *p*-toluenesulfonyl chloride). In part (ii) the product of part (i) is reacted with an excess of an aminating agent. Suitable aminating agents include ammonia (e.g. in the form of ammonium hydroxide) and ammonium salts (e.g., ammonium carbonate, ammonium bicarbonate, ammonium phosphate). The reaction can be carried out by dissolving a

compound of Formula XXIV in a suitable solvent such as dichloromethane or chloroform, adding ammonium hydroxide to the solution, and then adding *p*-toluenesulfonyl chloride. The protecting group is removed using known methods. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

In step (5) of Reaction Scheme III a 1*H*-imidazo[4,5-*c*]quinoline-4-amine of Formula XXV is reduced to provide a 6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinoline-4-amine of Formula XXVI. The reaction can be conveniently carried out by suspending or dissolving a compound of Formula XXV in ethanol, adding a catalytic amount of rhodium on carbon, and hydrogenating. The reaction can be carried out in a Parr apparatus. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

In step (6) of Reaction Scheme III a 6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinoline-4-amine of Formula XXVI is treated with *N*-hydroxyphthalimide under Mitsunobu reaction conditions to provide an *N*-phthalimide-protected 6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-2-yl hydroxylamine of Formula XXVII. The reaction is conveniently carried out by adding triphenylphosphine and *N*-hydroxyphthalimide to a solution of a compound of Formula XXVI in a suitable solvent such as tetrahydrofuran, and then slowly adding diethyl azodicarboxylate. The reaction can be carried out at ambient temperature or at an elevated temperature, such as 60 °C. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

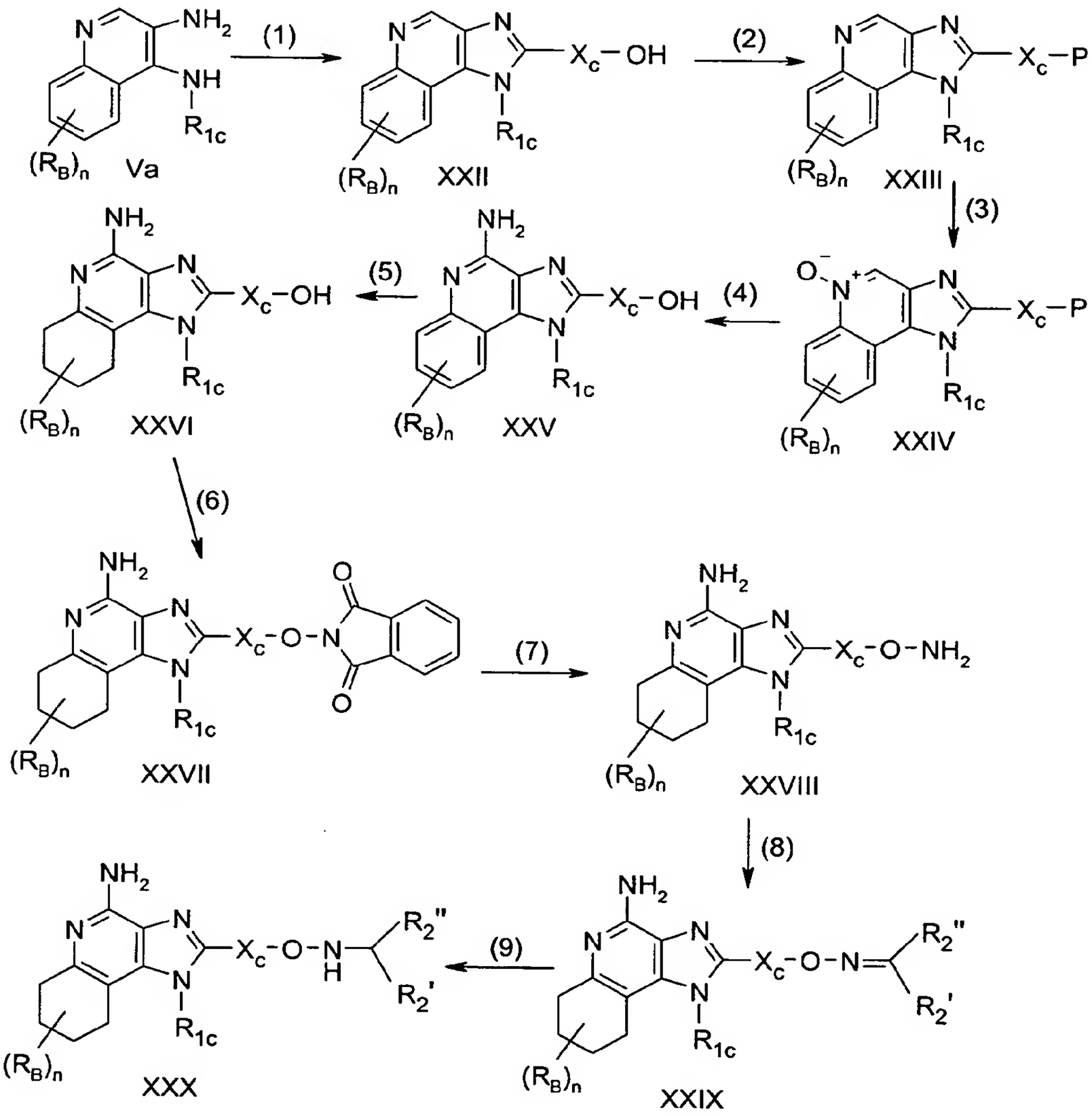
In step (7) of Reaction Scheme III an *N*-phthalimide-protected 6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-2-yl hydroxylamine of Formula XXVII is converted to a 6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-2-yl hydroxylamine of Formula XXVIII. Removal of the *N*-phthalimide protecting group is conveniently carried out by adding hydrazine to a suspension of an *N*-phthalimide-protected 6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-2-yl hydroxylamine of Formula XXVII in a suitable solvent such as ethanol. The reaction can be carried out at ambient temperature. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

In step (8) of Reaction Scheme III a 6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-2-yl hydroxylamine of Formula XXVIII is reacted with an aldehyde or ketone of formula $R_2'C(O)R_2''$ to provide a 6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-2-yl oxime of

Formula XXIX as in step (3) of Reaction Scheme II. The product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

In step (9) of Reaction Scheme III a 1*H*-imidazo[4,5-*c*]quinolin-2-yl oxime of Formula XXIX is reduced to provide a 1*H*-imidazo[4,5-*c*]quinolin-2-yl hydroxylamine of Formula XXX, which is a subgenus of Formulas II and IIa. The reduction is carried out as described in step (7) of Reaction Scheme I. The product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

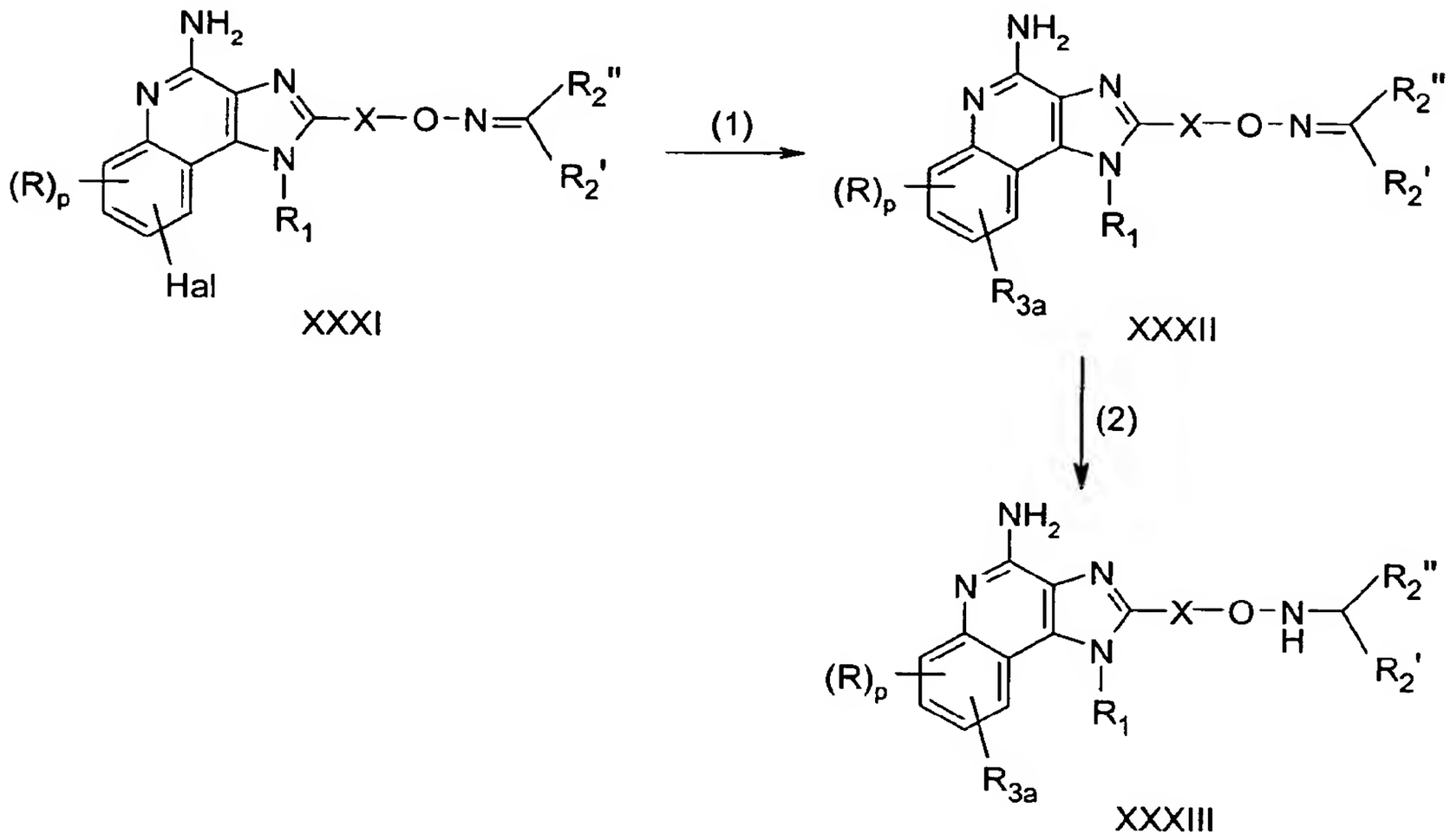
Reaction Scheme III



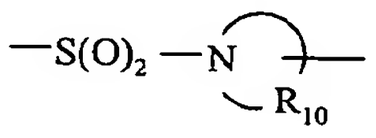
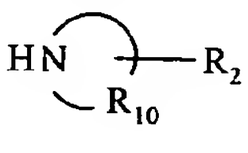
Compounds of the invention can be prepared according to Reaction Scheme IV where R_1, R, X, and Hal are as defined above, p is 0 to 3, R_2' and R_2" are the same as R_1' and R_1" as defined above, and R_{3a} is $-Z_a-Ar$, $-Z_a-Ar'-Y-R_4$, or $-Z_a-Ar'-X'-Y-R_4$ wherein Z_a is a bond, alkylene, or alkenylene, and Ar, Ar', Y, X', and R_4 are as defined above. In step (1) of Reaction Scheme IV a halogen substituted 1*H*-imidazo[4,5-*c*]quinolin-2-yl oxime of Formula XXXI is coupled with a boronic acid of the formula R_{3a}-$B(OH)_2$ (or the corresponding anhydride or esters, R_{3a}-$B(O\text{-alkyl})_2$, thereof) using Suzuki coupling conditions to provide a 1*H*-imidazo[4,5-*c*]quinolin-2-yl oxime of Formula XXXII. A compound of Formula XXXI is combined with a boronic acid of the formula R_{3a}-$B(OH)_2$ in the presence of palladium (II) acetate, triphenylphosphine and a base such as sodium carbonate in a suitable solvent such as n-propanol. The reaction can be carried out at an elevated temperature (e.g., 80-100°C). The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods. Halogen substituted 1*H*-imidazo[4,5-*c*]quinolin-2-yl oximes of Formula XXXI can be prepared as described above in steps (1)-(6) of Reaction Scheme I or steps (1) – (5) or (5a) or Reaction Scheme II, wherein one of the R groups is Hal.

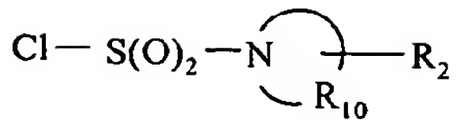
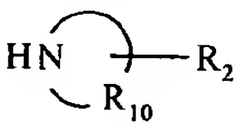
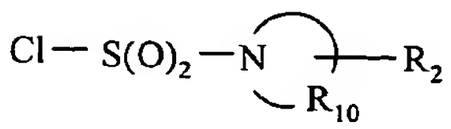
In step (2) of Reaction Scheme IV a 1*H*-imidazo[4,5-*c*]quinolin-2-yl oxime of Formula XXXII is reduced to provide a 1*H*-imidazo[4,5-*c*]quinolin-2-yl hydroxylamine of Formula XXXIII, which is a subgenus of Formulas I and Ia. The reduction is carried out as described in step (7) of Reaction Scheme I. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Reaction Scheme IV

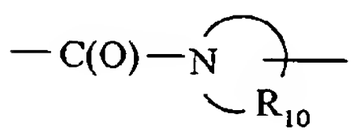
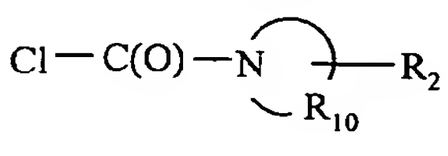


Compounds of the invention can be prepared according to Reaction Scheme V where R, R_1, R_2, X, and n are as defined above, and Y_a' is Y' defined above, excluding a bond. In step (1) of Reaction Scheme V, a 1*H*-imidazo[4,5-*c*]quinolin-2-yl hydroxylamine of Formula X is converted to a 1*H*-imidazo[4,5-*c*]quinolin-2-yl hydroxylamine of Formulas XXXIV, using conventional methods. For example, sulfonamides of Formula XXXIV (Y_a' is $-S(O)_2-$) can be prepared by reacting a compound of Formula X with a sulfonyl chloride of formula $R_2S(O)_2Cl$. The reaction can be carried out at ambient temperature in an inert solvent such as chloroform or dichloromethane by adding the sulfonyl chloride to a compound of Formula X in the presence of a base such as *N,N*-diisopropylethylamine, triethylamine, or pyridine.

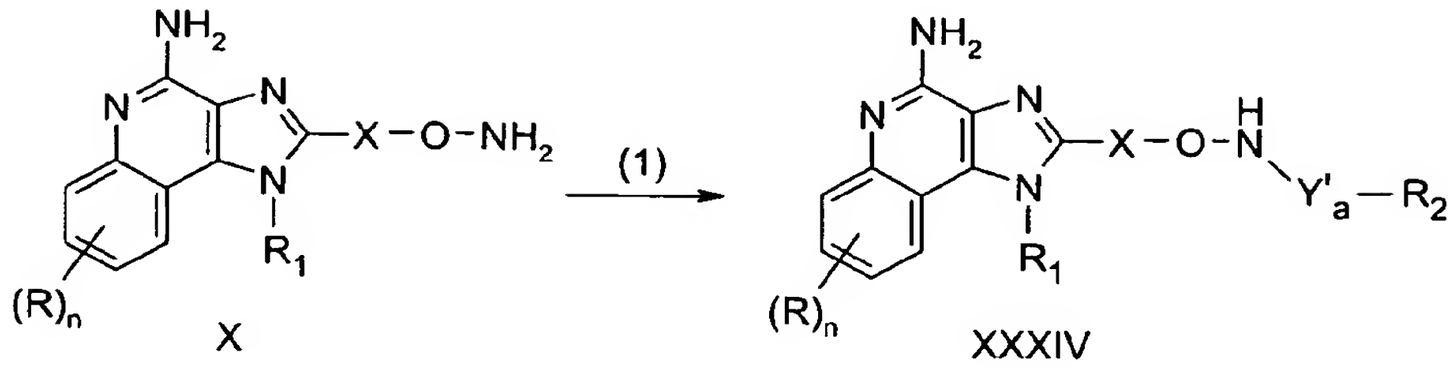
Sulfamides of Formula XXXIV (Y_a' is $-S(O)_2-N(R_8)-$ or ) can be prepared by reacting a compound of Formula X with sulfuryl chloride to generate a sulfamoyl chloride in situ, and then reacting the sulfamoyl chloride with an amine of formula $HN(R_8)R_2$, or  , or by reacting a compound of Formula X with a

sulfamoyl chloride of formula $R_2(R_8)NS(O)_2Cl$ or  . The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods. Many sulfonyl chlorides of formula $R_2S(O)_2Cl$, amines of formulas $HN(R_8)R_2$, and  , and some sulfamoyl chlorides of formulas $R_2(R_8)NS(O)_2Cl$ and  are commercially available; others can be prepared using known synthetic methods.

Amides of Formula XXXIV (Y_a' is –C(O)-) can be prepared from 1*H*-imidazo[4,5-*c*]quinolin-2-yl hydroxylamines of Formula X using conventional methods. For example, a compound of Formula X can be reacted with an acid chloride of formula $R_2C(O)Cl$ to provide a compound of Formula XXXIV. The reaction can be carried out by adding the acid chloride to a solution of a compound of Formula X in a suitable solvent such as chloroform, optionally in the presence of a base such as *N*,*N*-diisopropylethylamine, triethylamine, or pyridine, at ambient temperature. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Ureas and thioureas of Formula XXXIV (Y_a' is -C(O)-N(R_8)-, -C(S)-N(R_8)-, -C(O)-N(R_8)-S(O)$_2$-, -C(O)-N(R_8)-C(O)-, -C(S)-N(R_8)-C(O)-, or ) can be prepared from 1*H*-imidazo[4,5-*c*]quinolin-2-yl hydroxylamines of Formula X using conventional methods. For example, a compound of Formula X can be reacted with an isocyanate of formula $R_2N=C=O$. The reaction can be carried out by adding the isocyanate to a solution of a compound of Formula X in a suitable solvent such as chloroform, optionally in the presence of a base such as *N*,*N*-diisopropylethylamine, or triethylamine, at ambient temperature. Alternatively, a compound of Formula X can be reacted with a thioisocyanate of formula $R_2N=C=S$, a sulfonyl isocyanate of formula $R_2S(O)_2N=C=O$ or a carbamoyl chloride of formula $R_2NC(O)Cl$ or  . The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Reaction Scheme V

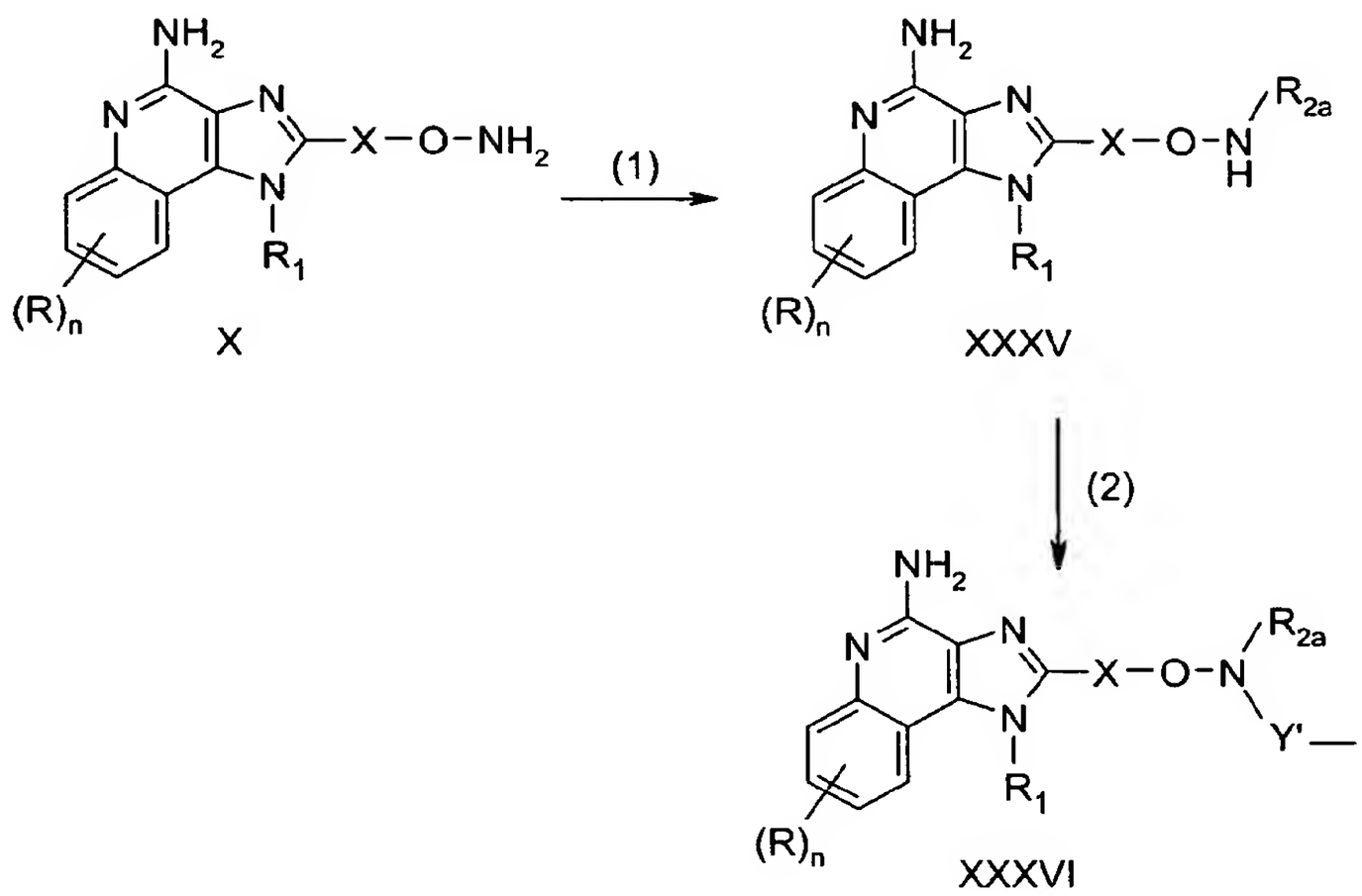


Compounds of the invention wherein R_{2a} is other than hydrogen can be prepared according to Reaction Scheme VI where R, R_1, R_2, X, Y', and n are as defined above.

In step (1) of Reaction Scheme VI, a 1*H*-imidazo[4,5-*c*]quinolin-2-yl hydroxylamine of Formula XXXV is prepared by reductive alkylation of a 1*H*-imidazo[4,5-*c*]quinolin-2-yl hydroxylamine of Formula X. The reaction is carried out in two steps, (i) reacting a compound of Formula X with the appropriate aldehyde to provide an oxime and (ii) reducing the oxime, using the methods of steps (6) and (7) respectively of Reaction Scheme I.

In step (2) of Reaction Scheme VI, a 1*H*-imidazo[4,5-*c*]quinolin-2-yl hydroxylamine of Formula XXXV is converted to a 1*H*-imidazo[4,5-*c*]quinolin-2-yl hydroxylamine of Formula XXXVI. Compounds of Formula XXXVI wherein Y' is a bond are prepared by subjecting the compound of Formula XXXV to a second alkylation. Compounds of Formula XXXVI wherein Y' is other than a bond are prepared using the methods of Reaction Scheme V. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Reaction Scheme VI



Pharmaceutical Compositions and Biological Activity

Pharmaceutical compositions of the invention contain a therapeutically effective amount of a compound of the invention as described above in combination with a pharmaceutically acceptable carrier.

The term "a therapeutically effective amount" or "effective amount" means an amount of the compound sufficient to induce a therapeutic or prophylactic effect, such as cytokine induction, immunomodulation, antitumor activity, and/or antiviral activity. Although the exact amount of active compound used in a pharmaceutical composition of the invention will vary according to factors known to those of skill in the art, such as the physical and chemical nature of the compound, the nature of the carrier, and the intended dosing regimen, it is anticipated that the compositions of the invention will contain sufficient active ingredient to provide a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μg/kg to about 5 mg/kg, of the compound to the subject. A variety of dosage forms may be used, such as tablets, lozenges, capsules, parenteral formulations, syrups, creams, ointments, aerosol formulations, transdermal patches, transmucosal patches and the like.

The compounds of the invention can be administered as the single therapeutic agent in the treatment regimen, or the compounds of the invention may be administered in combination with one another or with other active agents, including additional immune response modifiers, antivirals, antibiotics, antibodies, proteins, peptides, oligonucleotides, etc.

The compounds of the invention have been shown to induce the production of certain cytokines in experiments performed according to the tests set forth below. These results indicate that the compounds are useful as immune response modifiers that can modulate the immune response in a number of different ways, rendering them useful in the treatment of a variety of disorders.

Cytokines whose production may be induced by the administration of compounds according to the invention generally include interferon-α (IFN-α) and/or tumor necrosis factor-α (TNF-α) as well as certain interleukins (IL). Cytokines whose biosynthesis may be induced by compounds of the invention include IFN-α, TNF-α, IL-1, IL-6, IL-10 and IL-12, and a variety of other cytokines. Among other effects, these and other cytokines can inhibit virus production and tumor cell growth, making the compounds useful in the treatment of viral diseases and neoplastic diseases. Accordingly, the invention provides a method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or composition of the invention to the animal. The animal to which the compound or composition is administered for induction of cytokine biosynthesis may have a disease as described infra, for example a viral disease or a neoplastic disease, and administration of the compound may provide therapeutic treatment. Alternatively, the compound may be administered to the animal prior to the animal acquiring the disease so that administration of the compound may provide a prophylactic treatment.

In addition to the ability to induce the production of cytokines, the compounds of the invention affect other aspects of the innate immune response. For example, natural killer cell activity may be stimulated, an effect that may be due to cytokine induction. The compounds may also activate macrophages, which in turn stimulate secretion of nitric oxide and the production of additional cytokines. Further, the compounds may cause proliferation and differentiation of B-lymphocytes.

Compounds of the invention also have an effect on the acquired immune response. For example, the production of the T helper type 1 (Th1) cytokine IFN-γ is induced indirectly and the production of the T helper type 2 (Th2) cytokines IL-4, IL-5 and IL-13 are inhibited upon administration of the compounds.

Whether for prophylaxis or therapeutic treatment of a disease, and whether for effecting innate or acquired immunity, the compound or composition may be administered alone or in combination with one or more active components as in, for example, a vaccine adjuvant. When administered with other components, the compound and other component or components may be administered separately; together but independently such as in a solution; or together and associated with one another such as (a) covalently linked or (b) non-covalently associated, e.g., in a colloidal suspension.

Conditions for which IRMs identified herein may be used as treatments include, but are not limited to:

(a) viral diseases such as, for example, genital warts, common warts, plantar warts, hepatitis B, hepatitis C, molluscum contagiosum, and diseases resulting from infection by Variola, Herpes simplex virus (Type I and/or Type II), HIV, CMV, VZV, Rhinovirus, Adenovirus, Coronavirus, Influenza, or Para-influenza;

(b) bacterial diseases including, but not limited to, diseases resulting from infection by bacteria of, for example, the genus Escherichia, Enterobacter, Salmonella, Staphylococci, Shigella, Listeria, Aerobacter, Helicobacter, Klebsiella, Proteus, Pseudomonas, Streptococcus, Chlamydia, Mycoplasma, Pneumococcus, Neisseria, Clostridium, Bacillus, Corynebacterium, Mycobacterium, Campylobacter, Vibrio, Serratia, Providencia, Chromobacterium, Brucella, Yersinia, Haemophilus, or Bordetella;

(c) other infectious diseases, such as fungal diseases, leishmaniasis, chlamydia, candidiasis, aspergillosis, cryptococcal meningitis, pneumocystis carnii pneomonia, cryptosporidiosis, histoplasmosis, toxoplasmosis, and trypanosome infection;

(d) neoplastic diseases, such as intraepithelial neoplasias, cervical dysplasia, actinic keratosis, basal cell carcinoma, squamous cell carcinoma, hairy cell leukemia, Karposi's sarcoma, melanoma, renal cell carcinoma, myelogeous leukemia, multiple myeloma, non-Hodgkin's lymphoma, chronic lymphocytic leukemia, cutaneous T-cell lymphoma, B-cell lymphoma, and other cancers; and

(e) TH-2 mediated, atopic, and autoimmune diseases, such as atopic dermatitis or eczema, eosinophilia, asthma, allergy, allergic rhinitis, systemic lupus erythematosis, essential thrombocythaemia, multiple sclerosis, Ommen's syndrome, discoid lupus, alopecia areata, inhibition of keloid formation and other types of scarring, and enhancing would healing, including chronic wounds.

IRMs identified herein also may be useful as a vaccine adjuvant for use in conjunction with any material that raises either humoral and/or cell mediated immune response, such live viral and bacterial immunogens and inactivated viral, tumor-derived, protozoal, organism-derived, fungal, and bacterial immunogens, toxoids, toxins, polysaccharides, proteins, glycoproteins, peptides, cellular vaccines, DNA vaccines, recombinant proteins, glycoproteins, and peptides, and the like, for use in connection with, e.g., BCG, cholera, plague, typhoid, hepatitis A, B, and C, influenza A and B, parainfluenza, polio, rabies, measles, mumps, rubella, yellow fever, tetanus, diphtheria, hemophilus influenza b, tuberculosis, meningococcal and pneumococcal vaccines, adenovirus, HIV, chicken pox, cytomegalovirus, dengue, feline leukemia, fowl plague, HSV-1 and HSV-2, hog cholera, Japanese encephalitis, respiratory syncytial virus, rotavirus, papilloma virus, and yellow fever.

IRMs may also be particularly helpful in individuals having compromised immune function. For example, IRM compounds may be used for treating the opportunistic infections and tumors that occur after suppression of cell mediated immunity in, for example, transplant patients, cancer patients and HIV patients.

Thus, one or more of the above diseases or types of diseases, for example, a viral disease or a neoplastic disease may be treated in an animal in need thereof (having the disease) by administering a therapeutically effective amount of a compound or salt of formula (I) to the animal.

An amount of a compound effective to induce cytokine biosynthesis is an amount sufficient to cause one or more cell types, such as monocytes, macrophages, dendritic cells and B-cells to produce an amount of one or more cytokines such as, for example, IFN-α, TNF-α, IL-1, IL-6, IL-10 and IL-12 that is increased over the background level of such cytokines. The precise amount will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μg/kg to

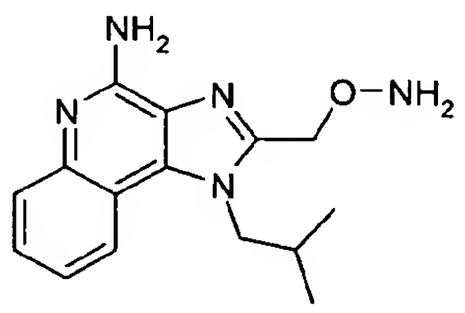
about 5 mg/kg. The invention also provides a method of treating a viral infection in an animal and a method of treating a neoplastic disease in an animal comprising administering an effective amount of a compound or composition of the invention to the animal. An amount effective to treat or inhibit a viral infection is an amount that will cause a reduction in one or more of the manifestations of viral infection, such as viral lesions, viral load, rate of virus production, and mortality as compared to untreated control animals. The precise amount that is effective for such treatment will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μg/kg to about 5 mg/kg. An amount of a compound effective to treat a neoplastic condition is an amount that will cause a reduction in tumor size or in the number of tumor foci. Again, the precise amount will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μg/kg to about 5 mg/kg.

Objects and advantages of this invention are further illustrated by the following examples, but the particular materials and amounts thereof recited in these examples, as well as other conditions and details, should not be construed to unduly limit this invention.

EXAMPLES

Example 1

O-{[4-Amino-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methyl}hydroxylamine



Part A

N^4-(2-Methylpropyl)quinoline-3,4-diamine (41 g), dichloromethane (550 mL), triethylamine (40 mL, 1.5 eq), and chloroacetyl chloride (16.7 mL, 1.1 eq.) were combined and then stirred at ambient temperature over the weekend. The reaction mixture was diluted with 1,2-dichloroethane (75 mL) and then washed with saturated aqueous sodium

bicarbonate (3 x 400 mL). The organic layer was dried over magnesium sulfate, filtered through a layer of CELITE filter aid, and then concentrated under reduced pressure to provide 52.81 g of 2-chloromethyl-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinoline as a brown solid.

Part B

3-Chloroperoxybenzoic acid (16.4 g of 77% max, 73.1 mmol) was added to a solution of 2-chloromethyl-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinoline (10 g, 36.5 mmol) in chloroform (250 mL). The reaction mixture was stirred at ambient temperature overnight. Ammonium hydroxide (100 mL) was added and the reaction was stirred vigorously for 15 minutes. *Para*-toluenesulfonyl chloride (8.4 g, 43.8 mmol) was added in portions over a period of 10 minutes. The reaction mixture was stirred at ambient temperature for 1 hour and then filtered to remove a precipitate. The filtrate was transferred to a separatory funnel and the layers were separated. The aqueous layer was extracted with dichloromethane (2 x 100 mL). The combined organics were dried over magnesium sulfate, filtered through a layer of CELITE filter aid, and then concentrated under reduced pressure to provide 16 g of crude product as a yellow foam. The foam was dissolved in 10% methanol in dichloromethane (20 mL). The solution was divided and loaded onto 2 BIOTAGE Flash 40 columns (90 g). The columns were eluted sequentially with 1L 1:1 ethyl acetate:hexanes, 2% methanol in 1:1 ethyl acetate:hexanes, and 5% methanol in 1:1 ethyl acetate:hexanes. The fractions containing product were combined and then concentrated under reduced pressure to provide 6.4 g of 2-chloromethyl-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine as an orange foam.

Part C

Triethylamine (536 mg, 5.19 mmol) was added to a solution of *N*-hydroxyphthalimide (678 mg, 4.16 mmol) in *N,N*-dimethylformamide (DMF); after 5 minutes a solution of 2-chloromethyl-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine (1 g) in DMF (10 mL) was added. The reaction mixture was stirred at ambient temperature for 2 hours. The reaction mixture was diluted with dichloromethane (50 mL) and then washed with water (1 x 100 mL). The aqueous layer was extracted with dichloromethane (2 x 50 mL) and ethyl acetate (1 x 50 mL). The combined organics were

dried over magnesium sulfate, filtered through a layer of CELITE filter aid, and then concentrated under reduced pressure to provide 1.8 g of crude product as a yellow solid. The solid was dissolved in 5% methanol in chloroform (10 mL) and loaded onto a BIOTAGE Flash 40 column (90 g). The column was eluted sequentially with 1L 1% methanol in chloroform and 3% methanol in chloroform. The fractions containing the desired product were combined and then concentrated under reduced pressure to provide 950 mg of a yellow solid. This material was recrystallized from acetonitrile, isolated by filtration, washed sequentially with acetonitrile and diethyl ether, and then dried in a vacuum oven at 65 °C overnight to provide 640 mg of 2-{[4-amino-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methoxy}isoindole-1,3-dione as a yellow crystalline solid, mp 221-222 °C.

^{1}H NMR (300 MHz, DMSO-d_6) δ 8.10 (d, J = 7.6 Hz, 1H), 7.88 (s, 4H), 7.63 (dd, J = 8.3 Hz, 1.2 Hz, 1H), 7.48 (m, 1H), 7.32 (m, 1H), 6.69 (br s, 2H), 5.51 (s, 2H), 4.73 (d, J = 7.6 Hz, 2H), 2.35 (m, 1H), 1.01 (d, J = 6.6 Hz, 6H);

MS (APCI) *m/z* 448.0 $(M + H)^+$;

Anal. Calc'd for $C_{23}H_{21}N_5O_3 \bullet 0.5CH_3CN \bullet 0.5H_2O$: C, 64.78; H, 5.32; N, 17.31. Found: C, 64.87; H, 5.28; N, 17.63.

Part D

Hydrazine (15 mL) was added to a solution of 2-{[4-amino-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methoxy}isoindole-1,3-dione (51 g of crude material from a large scale reaction) in ethanol (200 mL) and a precipitate formed almost immediately. The reaction mixture was stirred at ambient temperature for 1.5 hours and then filtered. The filter cake was washed with several portions of dichloromethane. The filtrate was concentrated under reduced pressure to provide 40 g of crude product as a brown semi-solid. The solid was partitioned between 1M aqueous hydrochloric acid (300 mL) and dichloromethane (100 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (2 x 100 mL). Analysis by liquid chromatography/mass spectroscopy (LCMS) showed that the organics did not contain product. The aqueous layer was made basic (pH ~10) with solid sodium carbonate and then extracted with dichloromethane (3 x 100 mL). The combined extracts were dried over magnesium sulfate, filtered, and then concentrated under reduced pressure to provide 9.29 g of product

as a brown foam. A portion (1.7 g) of this material was purified on a BIOTAGE Flash 40 column (40 g) eluting sequentially with 500 mL of 2%, 5%, 5%, and 10% methanol in ethyl acetate. The fractions containing product were combined and then concentrated under reduced pressure to provide 950 mg of an oil. The oil was dissolved in dichloromethane and then combined with 4M hydrochloric acid in dioxane. The resulting precipitate was isolated by filtration and then partitioned between dichloromethane (50 mL) and saturated aqueous sodium bicarbonate (50 mL). The aqueous layer was extracted with dichloromethane (3 x 50 mL). The combined organics were concentrated under reduced pressure to provide 500 mg of a foam. This material was dissolved in dichloromethane (50 mL) and then combined with 4M hydrochloric acid in dioxane (30 mL). A precipitate formed. The mixture was concentrated and then dissolved in hot ethanol. The solution was allowed to cool to ambient temperature, chilled (-10 °C) in a freezer overnight, and then allowed to warm to ambient temperature. A precipitate was isolated by filtration, washed with ethanol and acetonitrile, and then dried under high vacuum overnight to provide 261 mg of *O*-{[4-amino-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methyl}hydroxylamine dihydrochloride as a white crystalline solid, mp 205-207 °C.

^{1}H NMR (300 MHz, DMSO-d_6) δ 8.23 (d, J = 8.0 Hz, 1H), 7.86 (dd, J = 8.3 Hz, 1.0 Hz, 1H), 7.75 (dd, J = 7.3, 7.3 Hz, 1H), 7.62 (m, 1H), 5.57 (s, 2H), 4.64 (d, J = 7.6 Hz, 2H), 2.20 (m, 1H), 0.98 (d, J = 6.6 Hz, 6H);

^{13}C NMR (75 MHz, DMSO-d_6) δ 149.6, 149.2, 135.8, 134.4, 130.4, 125.5, 125.3, 122.7, 119.0, 112.9, 66.9, 52.5, 29.1, 19.3 (2);

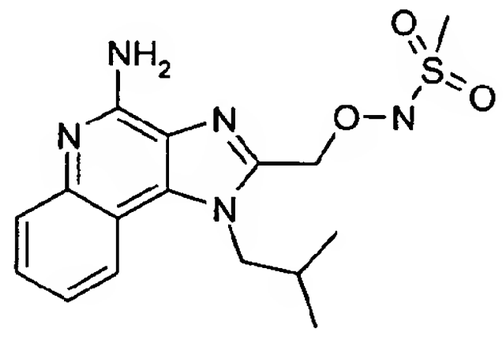
MS (APCI) *m/z* 286.1 $(M + H)^+$;

Anal. Calc'd for $C_{15}H_{19}N_5O \bullet 2.0\ HCl \bullet 0.3\ H_2O$: C, 49.54; H, 5.99; N, 19.26.

Found: C, 49.87; H, 6.36; N, 18.94.

Example 2

N-{[4-Amino-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methoxy}methanesulfonamide



Triethylamine (1.47 mL, 10.5 mmol) was added to a solution of *O*-{[4-amino-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methyl}hydroxylamine (1.5 g, 5.3 mmol) in dichloromethane (50 mL). Methanesulfonyl chloride (0.448 mL, 5.78 mmol) was added and the reaction mixture was stirred at ambient temperature for 2 hours. The reaction mixture was washed with saturated aqueous sodium bicarbonate (1 x 30 mL) and brine (1 x 30 mL), dried over magnesium sulfate, filtered, and then concentrated under reduced pressure to provide 2.16 g of crude product as a brown foam. This material was dissolved in dichloromethane (10 mL) and then loaded onto a BIOTAGE Flash 40 column (40 g). The column was eluted sequentially with 500 mL ethyl acetate, 2%, 3%, and 5% methanol in ethyl acetate. The fractions containing product were combined and then concentrated under reduced pressure to provide 850 mg of a yellow solid. The material was recrystallized from 3:2 ethanol:acetonitrile and dried under high vacuum to provide 206 mg of *N*-{[4-amino-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methoxy}methanesulfonamide as a yellow crystalline solid, mp 215-216 °C.

^{1}H NMR (300 MHz, DMSO-d_6) δ 10.3 (br s, 1H), 8.04 (d, J = 8.0 Hz, 1H), 7.63 (d, J = 7.4 Hz, 1H), 7.46 (m, 1H), 7.29 (m, 1H), 6.69 (br s, 2H), 5.23 (s, 2H), 4.50 (d, J = 7.6 Hz, 2H), 3.05 (s, 3H), 2.25 (m, 1H), 0.93 (d, J = 6.6 Hz, 6H);

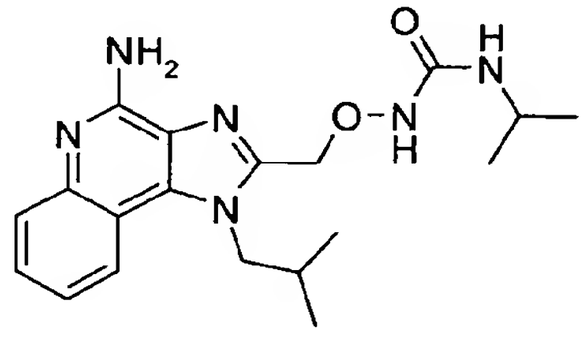
^{13}C NMR (75 MHz, DMSO-d_6) δ 152.9, 147.8, 146.3, 134.0, 127.9, 127.6, 127.3, 122.1, 121.5, 115.6, 70.9, 52.7, 37.6, 29.6, 20.1 (2);

MS (APCI) *m/z* 364.1 $(M + H)^+$;

Anal. Calc'd for $C_{16}H_{21}N_5O_3S$: C, 52.88; H, 5.82; N, 19.27. Found: C, 52.96; H, 5.81; N, 19.04.

Example 3

N-{[4-Amino-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methoxy}-*N'*-isopropylurea



Isopropyl isocyanate (0.620 mL, 6.31 mmol) was added to a solution of *O*-{[4-amino-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methyl}hydroxylamine (1.5 g, 5.3 mmol) in dichloromethane (50 mL). The reaction mixture was stirred at ambient temperature for 1 hour and then concentrated under reduced pressure to provide crude product as a brown foam. This material was dissolved in dichloromethane (10 mL) and then loaded onto a BIOTAGE Flash 40 column (40 g). The column was eluted sequentially with 500 mL 2%, 4%, 6%, and 8% methanol in ethyl acetate. The fractions containing product were combined and then concentrated under reduced pressure to provide 880 mg of a yellow solid. This solid was recrystallized from acetonitrile, isolated by filtration, washed with acetonitrile and diethyl ether, and then dried under high vacuum to provide 365 mg of *N*-{[4-amino-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methoxy}-*N'*-isopropylurea as a light yellow crystalline solid, mp 218-219 °C.

^{1}H NMR (300 MHz, DMSO-d_6) δ 9.21 (s, 1H), 8.02 (d, J = 8.1 Hz, 1H), 7.62 (d, J = 7.4 Hz, 1H), 7.45 (dd, J = 7.3, 7.3 Hz, 1H), 7.28 (dd, J = 7.1, 7.1 Hz, 1H), 6.66 (br s, 2H), 6.49 (d, J = 8.1 Hz , 1H), 5.07 (s, 2H), 4.49 (d, J = 7.5 Hz, 2H), 3.71 (m, 1H), 2.22 (m, 1H), 1.01 (d, J = 6.5 Hz, 6H), 0.93 (d, J = 6.6 Hz, 6H);

MS (APCI) *m/z* 371.1 $(M + H)^+$;

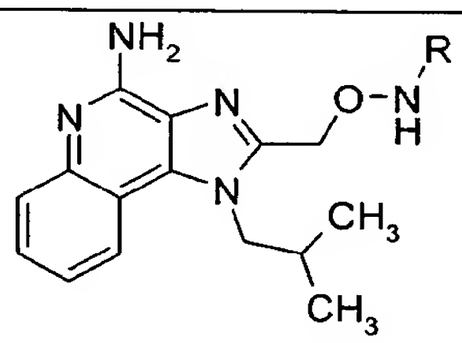
Anal. Calc'd for $C_{19}H_{26}N_6O_2$: C, 61.60; H, 7.07; N, 22.69.

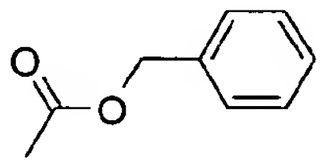
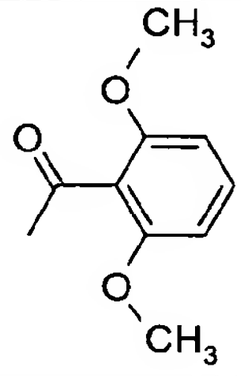
Found: C, 61.41; H, 7.40; N, 22.37.

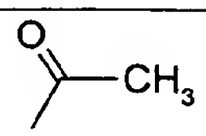
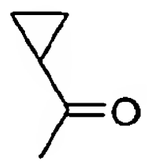
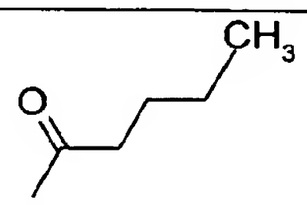
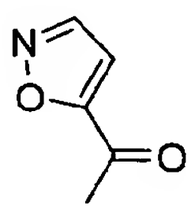
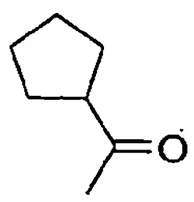
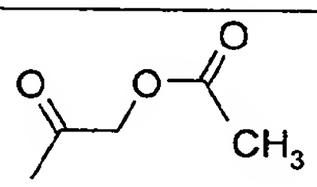
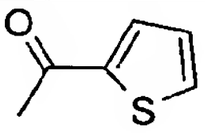
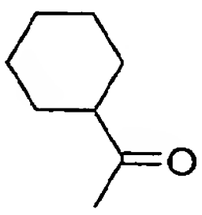
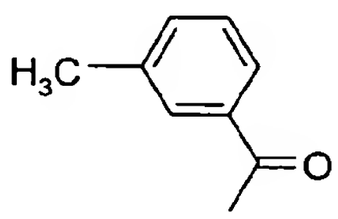
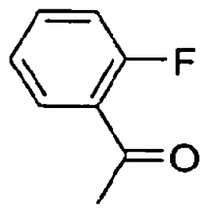
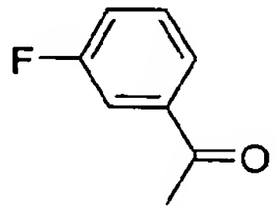
Examples 4 - 42

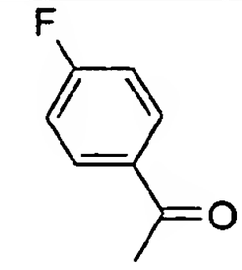
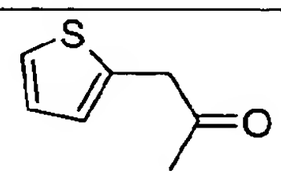
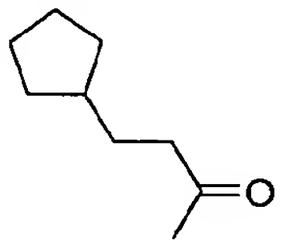
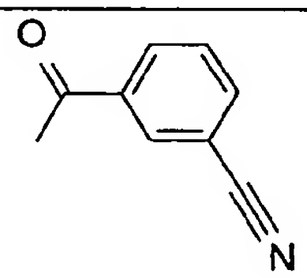
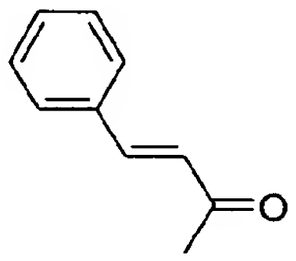
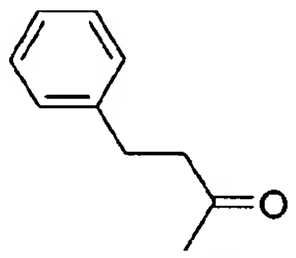
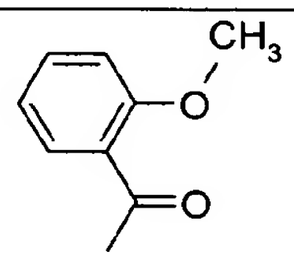
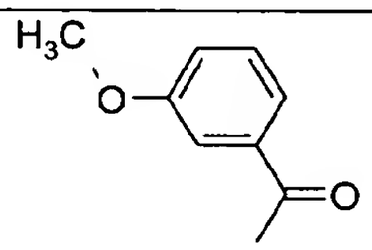
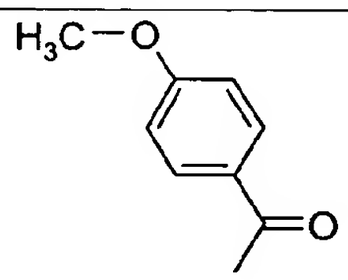
An acid chloride, sulfonyl chloride, sulfamoyl chloride, carbamoyl chloride or isocyanate from the table below (1.1 equivalents) was added to a test tube containing a

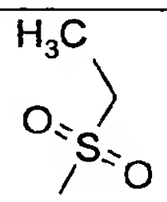
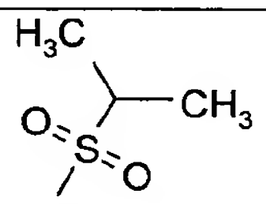
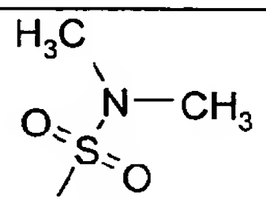
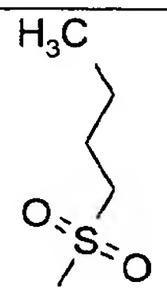
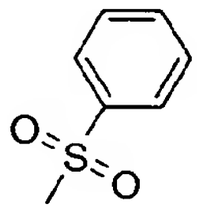
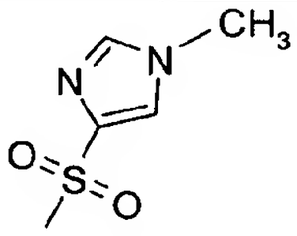
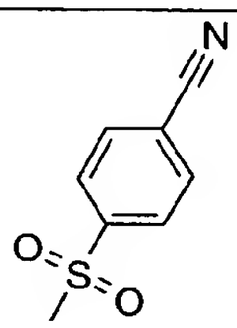
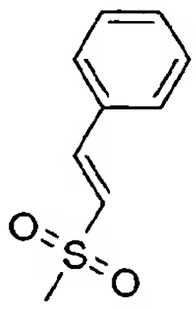
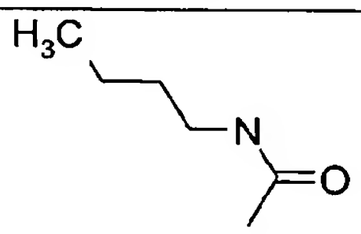
solution of O-{[4-amino-1-(2-methylpropyl)-1*H*-imidazo[4,5-c]quinolin-2-yl]methyl}hydroxylamine (30 mg) and triethylamine (2.0 eq.) in dichloromethane (1 mL). The test tube was capped and placed on a shaker at ambient temperature overnight (approximately 18 hours). The reaction was quenched by adding 2 drops of water and then vortexing the test tube. The solvent was removed by vacuum centrifugation. The compounds were purified by preparative high performance liquid chromatography (prep HPLC) using a Waters Fraction Lynx automated purification system. The prep HPLC fractions were analyzed using a Micromass LC-TOFMS, and the appropriate fractions were centrifuge evaporated to provide the trifluoroacetate salt of the desired compound. Column: Phenomenex Luna C18(2), 21.2 x 50 millimeters (mm), 10 micron particle size, 100 Angstroms (Å) pore; flow rate: 25 mL/min; non-linear gradient elution from 5-95% B in 9 min, then hold at 95% B for 2 min, where A is 0.05% trifluoroacetic acid/water and B is 0.05% trifluoroacetic acid/acetonitrile; fraction collection by mass-selective triggering. The table below shows the acid chloride, sulfonyl chloride, sulfamoyl chloride, carbamoyl chloride or isocyanate used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

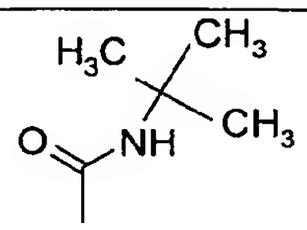
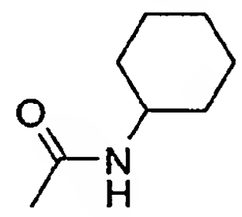
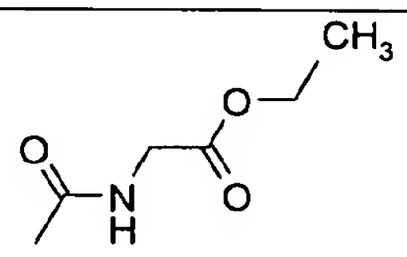
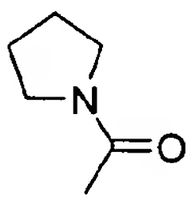
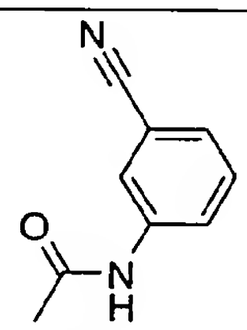
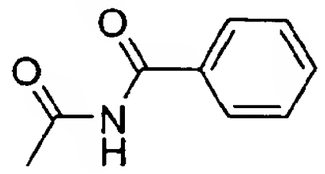
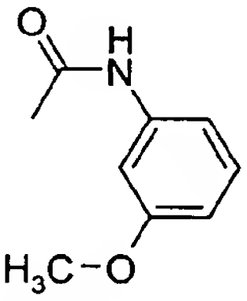
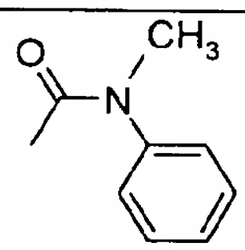


Example	Reagent	R	Measured Mass (M+H)
4	Benzyloxy chloroformate		420.2029
5	2,6-Dimethoxybenzoyl chloride		450.2139

6	Acetyl chloride		328.1793
7	Cyclopropanecarbonyl chloride		354.1964
8	Pentanoyl chloride		370.2253
9	Isoxazole-5-carbonyl chloride		381.1691
10	Cyclopentanecarbonyl chloride		382.2254
11	Acetoxyacetyl chloride		386.1861
12	Thiophene-2-carbonyl chloride		396.1524
13	Cyclohexanecarbonyl chloride		396.2410
14	*m*-Toluoyl chloride		404.2123
15	2-Fluorobenzoyl chloride		408.1862
16	3-Fluorobenzoyl chloride		408.1859

17	4-Fluorobenzoyl chloride		408.1833
18	2-Thiopheneacetyl chloride		410.1675
19	3-Cyclopentylpropionyl chloride		410.2574
20	3-Cyanobenzoyl chloride		415.1883
21	Cinnamoyl chloride		416.2099
22	Hydrocinnamoyl chloride		418.2263
23	2-Methoxybenzoyl chloride		420.2025
24	3-Methoxybenzoyl chloride		420.2057
25	4-Methoxybenzoyl chloride		420.2047

26	Ethanesulfonyl chloride		378.1633
27	Isopropylsulfonyl chloride		392.1779
28	Dimethylsulfamoyl chloride		393.1730
29	1-Butanesulfonyl chloride		406.1936
30	Benzenesulfonyl chloride		426.1626
31	1-Methylimidazole-4-sulfonyl chloride		430.1666
32	4-Cyanobenzenesulfonyl chloride		451.1553
33	*Beta*-styrenesulfonyl chloride		452.1757
34	*n*-Butyl isocyanate		385.2363

35	*Tert*-Butyl isocyanate		385.2388
36	Cyclohexyl isocyanate		411.2525
37	Ethyl isocyanatoacetate		415.2110
38	1-Pyrrolidinecarbonyl chloride		383.2214
39	3-Cyanophenyl isocyanate		430.2019
40	Benzoyl isocyanate		433.1987
41	3-Methoxyphenyl isocyanate		435.2169
42	*N*-Methyl *N*-phenylcarbamoyl chloride		419.2201

Examples 43 - 68

Part A

Triethylamine (9 mL, 64.7 mmol) was added to a solution of *tert*-butyl [3-(3-aminoquinolin-4-ylamino)propyl]carbamate (13.65 g, 43.1 mmol) in dichloromethane (150 mL). Chloroacetyl chloride (3.8 mL, 47.5 mmol) was added dropwise over a period of 10

minutes. The reaction mixture was stirred at ambient temperature over the weekend and then concentrated under reduced pressure. The residue was partitioned between ethyl acetate (100 mL) and 1:1 water:saturated aqueous sodium bicarbonate. The organic layer was washed with brine (100 mL). The combined aqueous layers were extracted with ethyl acetate (2 x 100 mL). The combined organics were dried over magnesium sulfate, filtered, and then concentrated under reduced pressure to provide 14.1 g of crude product as a brown foam. The foam was dissolved in a mixture of dichloromethane (15 mL) and methanol (0.5 mL). The solution was divided and loaded onto 2 BIOTAGE Flash 40 (90 g) columns. The columns were eluted sequentially with 1 L 1:1 ethyl acetate:hexanes, 5% methanol in 1:1 ethyl acetate:hexanes, and 10% methanol in 1:1 ethyl acetate:hexanes. The fractions containing product were combined and concentrated under reduced pressure to provide 8.96 g of tert-butyl [3-(2-chloromethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]carbamate as a light brown foam.

Part B

3-Chloroperoxybenzoic acid (13.3 g of 77% max, 59.4 eq.) was added in portions over a period of 5 minutes to a solution of *tert*-butyl [3-(2-chloromethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]carbamate (8.9 g, 23.7 mmol) in chloroform (200 mL). The reaction mixture was allowed to stir at ambient temperature overnight. Ammonium hydroxide (50 mL) was added and the reaction mixture was stirred vigorously. *Para*-toluensulfonyl chloride (5.43 g, 28.5 mmol) was added over a period of 5 minutes. The reaction mixture was stirred at ambient temperature for 2 hours; an additional 1 g of *para*-toluensulfonyl chloride was added and the reaction mixture was stirred for another hour. The reaction mixture was filtered to remove solids. The filtrate was transferred to a separatory funnel and the layers were separated. The organic layer was washed with 1:1 water:saturated aqueous sodium bicarbonate (2 x 150 mL). The combined aqueous was extracted with dichloromethane (2 x 150 mL) and ethyl acetate (1 x 100 mL). The combined organic extracts were concentrated under reduced pressure to provide 13.6 g of crude product as a brown foam. The foam was dissolved in dichloromethane (20 mL). The solution was divided and loaded onto 2 BIOTAGE Flash 40 columns (90 g). The first column was eluted sequentially with 1L 1:1 ethyl acetate:hexanes, 5% methanol in 1:1 ethyl acetate:hexanes, and 10% methanol in 1:1 ethyl acetate:hexanes. The second column

was eluted sequentially with 1L 1:1 ethyl acetate:hexanes, 7% methanol in 1:1 ethyl acetate:hexanes, and 7% methanol in 1:1 ethyl acetate:hexanes. The fractions containing product were combined and then concentrated under reduced pressure to provide 4.3 g of *tert*-butyl [3-(4-amino-2-chloromethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]carbamate as a light yellow foam.

Part C

Triethylamine (4.6 mL, 33.1 mmol) was added to a solution of *N*-hydroxyphthalimide (2.16 g, 13.2 mmol) in DMF (10 mL). A solution of *tert*-butyl [3-(4-amino-2-chloromethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]carbamate (4.3 g, 11.0 mmol) in DMF (20 ml) was added. The reaction was stirred at ambient temperature for 3.5 hours and then diluted with water (100 mL). The resulting precipitate was isolated by filtration, washed with water, and then dried in a vacuum oven at 60°C over the weekend to provide 4.25 g of *tert*-butyl (3-{4-amino-2-[(1,3-dioxo-1,3-dihydroisoindol-2-yl)oxymethyl]-1*H*-imidazo[4,5-*c*]quinolin-1-yl}propyl)carbamate as a light yellow solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 8.2 (d, J = 8.0 Hz, 1H), 7.9 (s, 4H), 7.7 (m, 1H), 7.5 (m, 1H), 7.3 (m, 1H), 7.2 (m, 1H), 6.7 (br s, 2H), 5.5 (s, 2H), 4.8 (m, 2H), 3.2 (m, 2H), 2.2 (m, 2H), 1.4 (s, 9H);

MS (APCI) m/z 517.3 $(M + H)^+$.

Part D

Hydrazine hydrate (8 mL of 55%) was added to a suspension of *tert*-butyl (3-{4-amino-2-[(1,3-dioxo-1,3-dihydroisoindol-2-yl)oxymethyl]-1*H*-imidazo[4,5-*c*]quinolin-1-yl}propyl)carbamate (4.25 g, 8.23 mmol) in ethanol (70 mL). The reaction became homogeneous after about 2 minutes. A precipitate started forming after about 1 hour. After stirring at ambient temperature for a total of 2 hours the reaction mixture was filtered and the filter cake was washed with dichloromethane. The filtrate was concentrated under reduced pressure. The residue was azeotroped twice with toluene to provide 3.63 g of *tert*-butyl [3-(4-amino-2-aminooxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]carbamate as a white solid.

Part E

Acetone (20 mL) was added to a solution of *tert*-butyl [3-(4-amino-2-aminooxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]carbamate (3.6 g) in methanol

(70 mL). The reaction mixture was stirred at ambient temperature overnight and then concentrated under reduced pressure to provide 4.12 g of *tert*-butyl [3-(4-amino-2-isopropylideneaminoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]carbamate as a light yellow foam.

Part F

Trifluoroacetic acid (7 mL) was added to a suspension of *tert*-butyl [3-(4-amino-2-isopropylideneaminoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]carbamate (4.12 g) in dichloromethane (70 mL). The reaction became homogeneous and was stirred at ambient temperature for 2.5 hours. More trifluoroacetic acid (10 mL) was added and the reaction was stirred for another hour. The reaction mixture was concentrated under reduced pressure and placed under high vacuum overnight to provide 7.68 g of propan-2-one O-{[4-amino-1-(3-aminopropyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methyl}oxime a white solid. Based on the weight this material was assumed to contain 5 equivalents of trifluoroacetic acid.

Part G

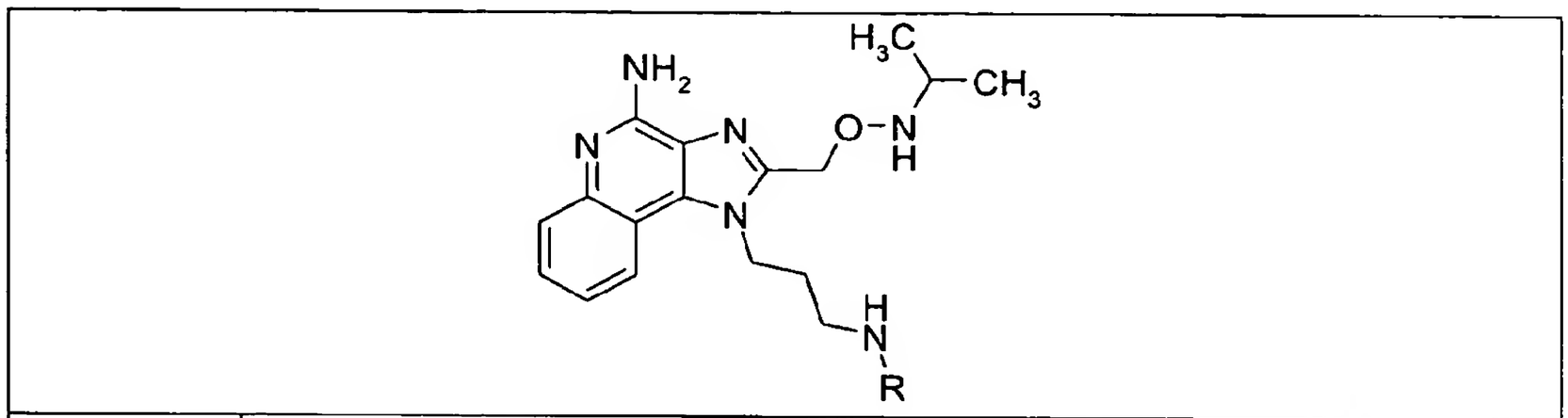
An acid chloride, sulfonyl chloride, sulfamoyl chloride, carbamoyl chloride or isocyanate from the table below (1.1 equivalents) was added to a test tube containing propan-2-one O-{[4-amino-1-(3-aminopropyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methyl}oxime trifluoroacetate (~90 mg) prepared in Part F, *N*,*N*-diisopropylethylamine (350 µL, 10 equivalents), and chloroform (2 mL). The test tube was capped and placed on a shaker at ambient temperature overnight (approximately 18 hours). Water (1 drop) was added to the test tube and then the solvent was removed by vacuum centrifugation. The residue was dissolved in methanol (5 mL).

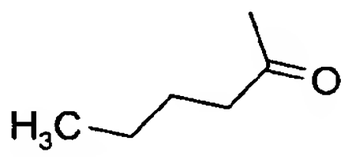
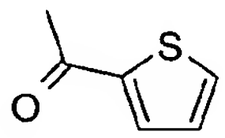
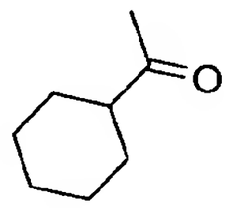
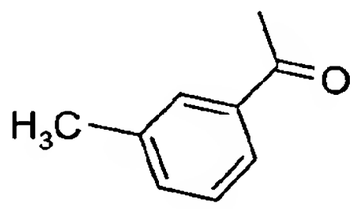
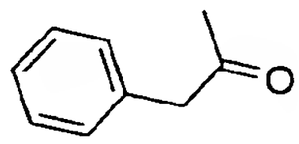
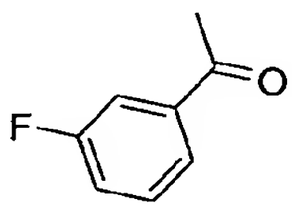
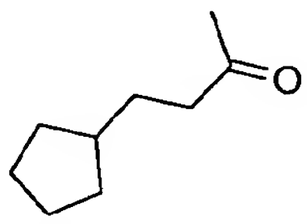
Part H

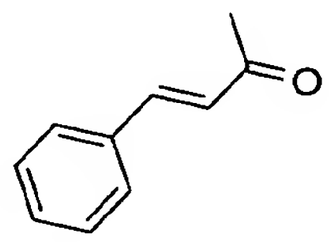
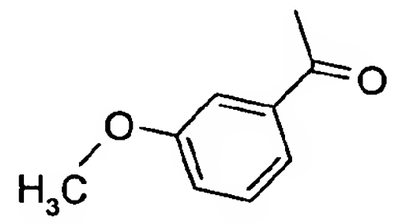
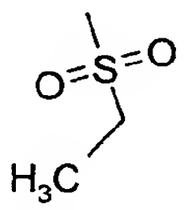
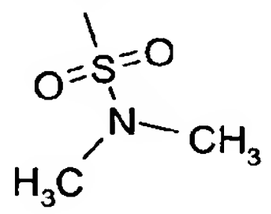
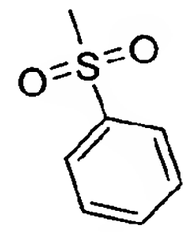
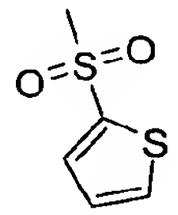
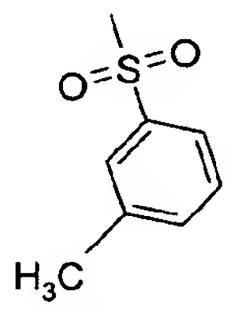
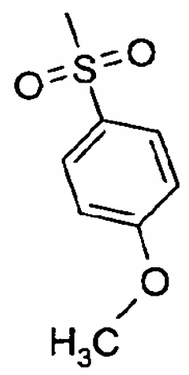
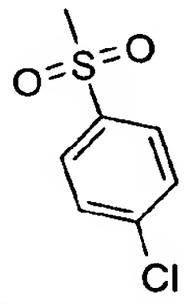
A portion (2.5 mL) of the solution from Part G was transferred to a fresh test tube and then the solvent was removed by vacuum centrifugation. Methanol (1 mL), glacial acetic acid (1 mL), and 400 µL of a 1.0 M solution of sodium cyanoborohydride in tetrahydrofuran were added to the test tube. The test tube was capped and placed on a shaker at ambient temperature overnight (approximately 18 hours). The solvent was removed by vacuum centrifugation. The compounds were purified by preparative high performance liquid chromatography (prep HPLC) using a Waters Fraction Lynx automated

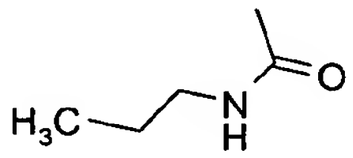
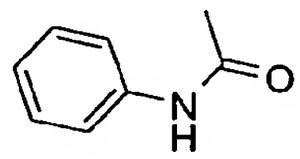
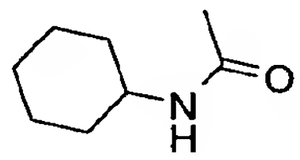
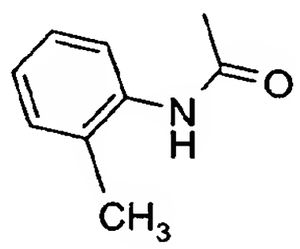
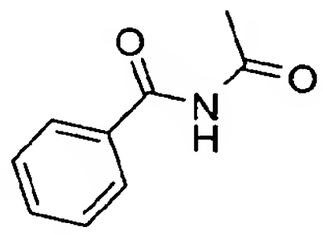
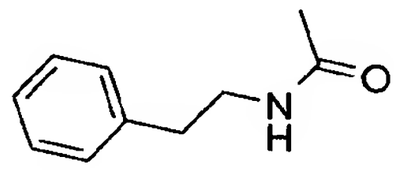
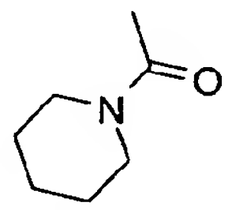
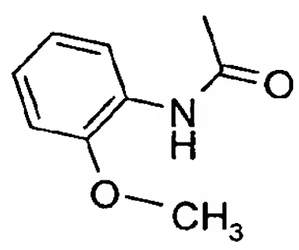
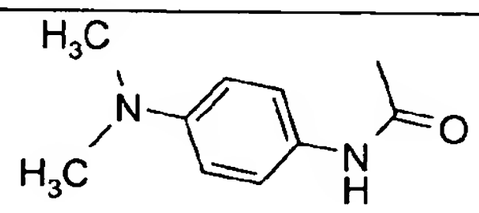
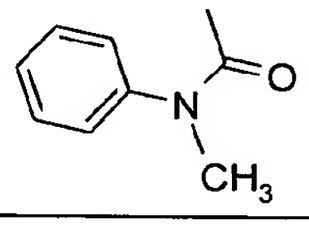
purification system using the method described above for Examples 4 - 42. The table below shows the acid chloride, sulfonyl chloride, sulfamoyl chloride, carbamoyl chloride or isocyanate used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

5



Example	Reagent	R	Measured Mass (M+H)
43	Pentanoyl chloride		413.2688
44	Thiophene-2-carbonyl chloride		439.1887
45	Cyclohexanecarbonyl chloride		439.2802
46	*m*-Toluoyl chloride		447.2496
47	Phenylacetyl chloride		447.2506
48	3-Fluorobenzoyl chloride		451.2300
49	3-Cyclopentanepropionyl chloride		453.2965

50	Cinnamoyl chloride		459.2536
51	*m*-Anisoyl chloride		463.2481
52	Ethanesulfonyl chloride		421.2022
53	Dimethylsulfamoyl chloride		436.2159
54	Benzenesulfonyl chloride		469.2024
55	2-Thiophenesulfonyl chloride		475.1577
56	3-Methylbenzenesulfonyl chloride		483.2185
57	4-Methoxybenzenesulfonyl chloride		499.2121
58	4-Chlorobenzensulfonyl chloride		503.1618

59	*n*-Propyl isocyanate		414.2620
60	Phenyl isocyanate		448.2486
61	Cyclohexyl isocyanate		454.2916
62	*o*-Tolyl isocyanate		462.2619
63	Benzoyl isocyanate		476.2406
64	2-Phenylethyl isocyanate		476.2772
65	1-Piperidinecarbonyl chloride		440.2767
66	2-Methoxyphenyl isocyanate		478.2539
67	4-Dimethylaminophenyl isocyanate		491.2894
68	*N*-Methyl *N*-phenylcarbamoyl chloride		462.2595

Examples 69 - 97

Part A

Using the general method of Examples 43 - 68 Part A, *tert*-butyl [2-(3-aminoquinolin-4-ylamino)ethyl]carbamate (43.5 g, 144 mmol) was reacted with chloroacetyl chloride (17.72 g, 158 mmol) to provide 37.39 g of *tert*-butyl [2-(2-chloromethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethyl]carbamate.

Part B

Using the general method of Examples 43 - 68 Part B, a solution of *tert*-butyl [2-(2-chloromethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethyl]carbamate (27.45 g, 76.1 mmol) in chloroform (500 mL) was treated with 3-chloroperoxybenzoic acid (25.6 g of 77% max, 114 mmol) and the resulting 5-oxide was aminated using ammonium hydroxide (150 mL) and *para*-toluenesulfonyl chloride (17.4 g, 91.3 mmol) to provide 41.83 g of crude *tert*-butyl [2-(4-amino-2-chloromethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethyl]carbamate as a brown solid. A portion (~32 g) of the crude material was dissolved in dichloromethane and then washed with 1 N hydrochloric acid (x3). The organic layer was allowed to stand for several days and a precipitate formed. This material was isolated by filtration to provide 7.0 g of *tert*-butyl [2-(4-amino-2-chloromethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethyl]carbamate as an off white solid.

Part C

Using the general method of Examples 43 - 68 Part C, *tert*-butyl [2-(4-amino-2-chloromethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethyl]carbamate (7 g, 19 mmol)) was reacted with *N*-hydroxyphthalimide (3.65 g, 22.3 mmol) to provide 6.37 g of *tert*-butyl (2-{4-amino-2-[(1,3-dioxo-1,3-dihydroisoindol-2-yl)oxymethyl]-1*H*-imidazo[4,5-*c*]quinolin-1-yl}ethyl)carbamate as a yellow solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 8.3 (d, J = 8.5 Hz, 1H), 7.9 (s, 4H), 7.6 (m, 1H), 7.5 (m, 1H), 7.3 (m, 1H), 7.1 (m, 1H), 6.6 (br s, 2H), 5.5 (s, 2H), 4.9 (m, 2H), 3.6 (m, 2H), 1.3 (s, 9H);

MS (APCI) m/z 503.2 $(M + H)^+$.

Part D

Using the general method of Examples 43 - 68 Part D, the *N*-phthalimide protecting group was removed from *tert*-butyl (2-{4-amino-2-[(1,3-dioxo-1,3-

dihydroisoindol-2-yl)oxymethyl]-1*H*-imidazo[4,5-*c*]quinolin-1-yl}ethyl)carbamate (6.35 g) to provide crude *tert*-butyl [2-(4-amino-2-aminooxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethyl]carbamate.

Part E

Acetone (25 mL) was added to a suspension of the crude material from Part D in methanol (100 mL). The resulting solution was stirred at ambient temperature for 3 hours and then concentrated under reduced pressure. The residue was azeotroped once with toluene, slurried with ethanol (100 mL) and then filtered. The filter cake was washed with additional ethanol. The filtrate was concentrated under reduced pressure to provide 3.9 g of product as a yellow solid. Additional product (0.9 g) was obtained by extracting the filter cake with dichloromethane. The two lots were combined to provide 4.8 g of *tert*-butyl [2-(4-amino-2-isopropylideneaminooxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethyl]carbamate.

Part F

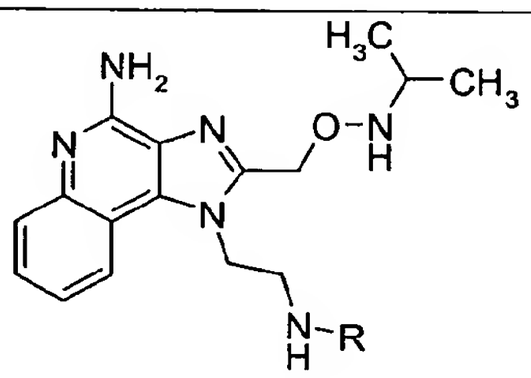
Trifluoroacetic acid (10 mL) was added to a suspension of *tert*-butyl [2-(4-amino-2-isopropylideneaminooxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethyl]carbamate (4.8 g) in dichloromethane (100 mL). The reaction became homogeneous and was stirred at ambient temperature. At 2.5 hours and 3.5 hours more trifluoroacetic acid (10 mL and 5 mL respectively) was added. After a total reaction time of 4 hours the reaction mixture was concentrated under reduced pressure. The residue was azeotroped with toluene (x3) and then placed under high vacuum overnight to provide 9.97 g of propan-2-one O-{[4-amino-1-(2-aminoethyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methyl}oxime as a yellow solid. Based on the weight this material was assumed to contain 5 equivalents of trifluoroacetic acid.

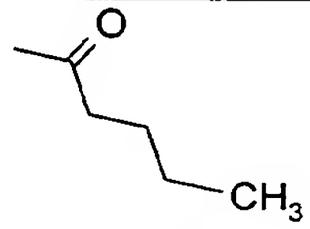
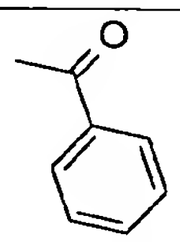
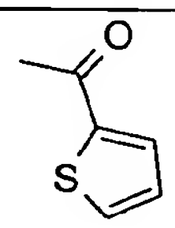
Part G

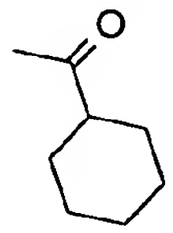
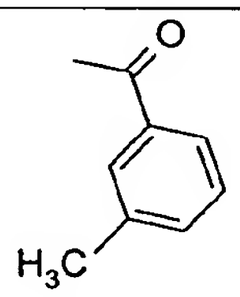
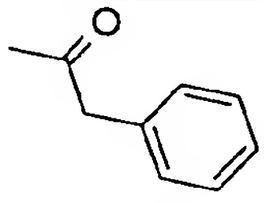
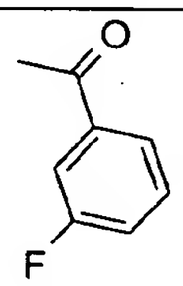
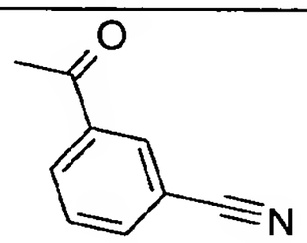
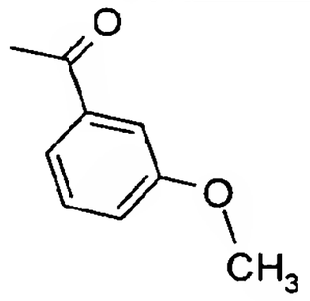
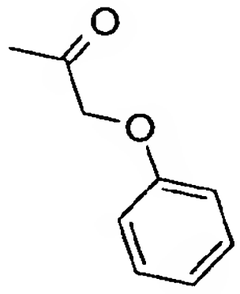
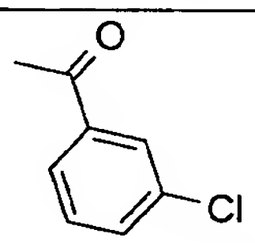
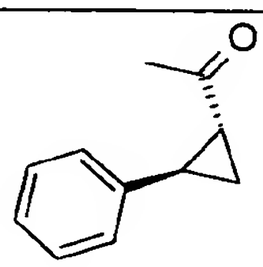
An acid chloride, sulfonyl chloride, sulfamoyl chloride, carbamoyl chloride or isocyanate from the table below (1.1 equivalents) was added to a test tube containing propan-2-one O-{[4-amino-1-(2-aminoethyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methyl}oxime trifluoroacetate (~90 mg) prepared in Part F, *N*,*N*-diisopropylethylamine (350 µL, 10 equivalents), and chloroform (2 mL). The test tube was capped and placed on a shaker at ambient temperature overnight (approximately 18 hours).

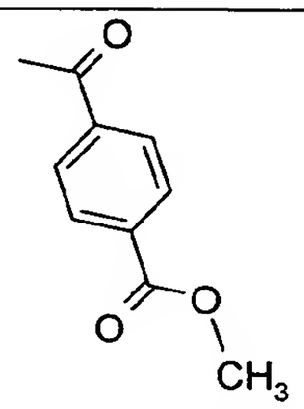
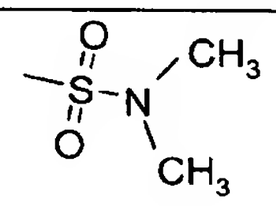
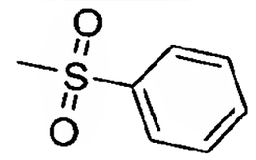
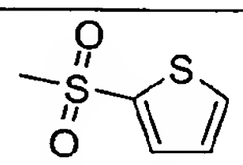
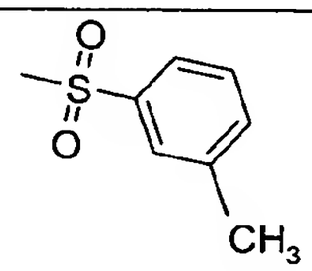
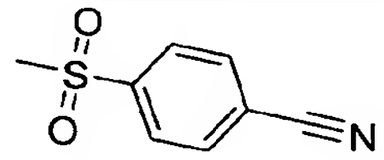
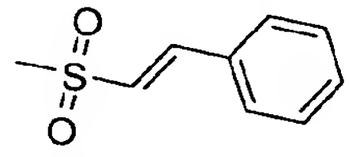
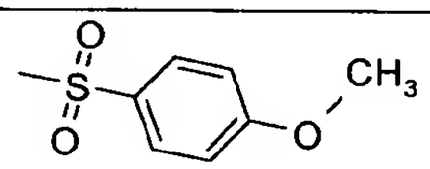
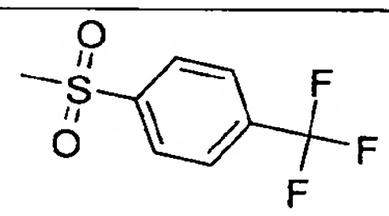
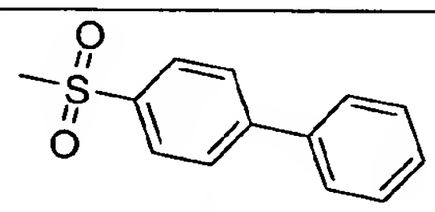
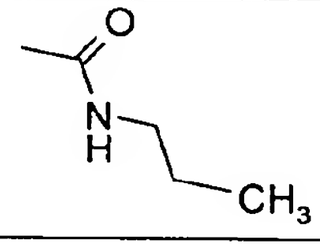
Part H

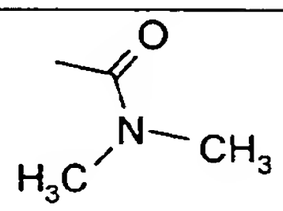
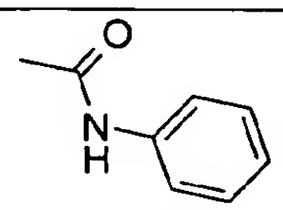
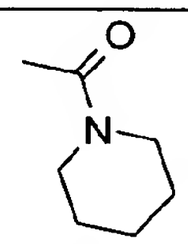
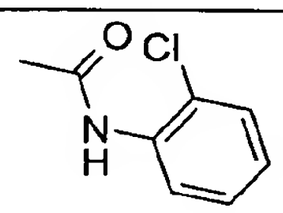
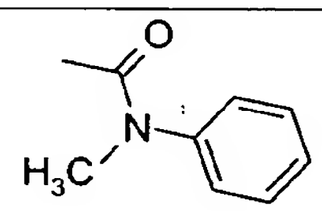
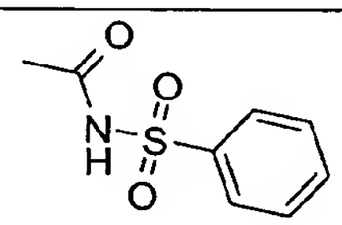
A portion (1 mL) of the solution from Part G was transferred to a fresh test tube and then the solvent was removed by vacuum centrifugation. Methanol (1 mL), glacial acetic acid (1 mL), and 300 μL of a 1.0 M solution of sodium cyanoborohydride in tetrahydrofuran were added to the test tube. The test tube was capped and placed on a shaker at ambient temperature overnight (approximately 18 hours). The solvent was removed by vacuum centrifugation. The compounds were purified by preparative high performance liquid chromatography (prep HPLC) using a Waters Fraction Lynx automated purification system using the method described above for Examples 4 - 42. The table below shows the acid chloride, sulfonyl chloride, sulfamoyl chloride, carbamoyl chloride or isocyanate used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.



Example	Reagent	R	Measured Mass (M+H)
69	Pentanoyl chloride		399.2517
70	Benzoyl chloride		419.2220
71	Thiophene-2-carbonyl chloride		425.1739

72	Cyclohexanecarbonyl chloride		425.2692
73	*m*-Toluoyl chloride		433.2369
74	Phenylacetyl chloride		433.2391
75	3-Fluorobenzoyl chloride		437.2117
76	3-Cyanobenzoyl chloride		444.2170
77	*m*-Anisoyl chloride		449.2313
78	Phenoxyacetyl chloride		449.2321
79	3-Chlorobenzoyl chloride		453.1832
80	*Trans*-2-Phenyl-1-cyclopropanecarbonyl chloride		459.2547

81	Methyl 4-chlorocarbonyl benzoate		477.2285
82	Dimethylsulfamoyl choride		422.1976
83	Benzenesulfonyl chloride		455.1888
84	2-Thiophenesulfonyl chloride		461.1451
85	3-Methylbenzenesulfonyl chloride		469.2006
86	4-Cyanobenzenesulfonyl chloride		480.1805
87	*Beta*-Styrenesulfonyl chloride		481.2017
88	4-Methoxybenzenesulfonyl chloride		485.1993
89	4-Trifluoromethyl benzenesulfonyl chloride		523.1732
90	4-Biphenylsulfonyl chloride		531.2167
91	*n*-Propyl isocyanate		400.2466

92	*N*,*N*-Dimethylcarbamoyl chloride		386.2315
93	Phenyl isocyanate		434.2301
94	1-Piperidinecarbonyl chloride		426.2625
95	2-Chlorophenyl isocyanate		468.1926
96	*N*-Methyl *N*-phenylcarbamoyl chloride		448.2464
97	Benzenesulfonyl isocyanate		498.1898

CYTOKINE INDUCTION IN HUMAN CELLS

Compounds of the invention have been found to induce cytokine biosynthesis when tested using the method described below.

An in vitro human blood cell system is used to assess cytokine induction. Activity is based on the measurement of interferon and tumor necrosis factor (α) (IFN and TNF, respectively) secreted into culture media as described by Testerman et. al. in "Cytokine Induction by the Immunomodulators Imiquimod and S-27609", Journal of Leukocyte Biology, 58, 365-372 (September, 1995).

Blood Cell Preparation for Culture

Whole blood from healthy human donors is collected by venipuncture into EDTA vacutainer tubes. Peripheral blood mononuclear cells (PBMC) are separated from whole blood by density gradient centrifugation using HISTOPAQUE-1077. Blood is diluted 1:1

with Dulbecco's Phosphate Buffered Saline (DPBS) or Hank's Balanced Salts Solution (HBSS). The PBMC layer is collected and washed twice with DPBS or HBSS and resuspended at 4 x 10^6 cells/mL in RPMI complete. The PBMC suspension is added to 48 well flat bottom sterile tissue culture plates (Costar, Cambridge, MA or Becton Dickinson Labware, Lincoln Park, NJ) containing an equal volume of RPMI complete media containing test compound.

Compound Preparation

The compounds are solubilized in dimethyl sulfoxide (DMSO). The DMSO concentration should not exceed a final concentration of 1% for addition to the culture wells. The compounds are generally tested at concentrations ranging from 30-0.014 μM.

Incubation

The solution of test compound is added at 60 μM to the first well containing RPMI complete and serial 3 fold dilutions are made in the wells. The PBMC suspension is then added to the wells in an equal volume, bringing the test compound concentrations to the desired range (30-0.014 μM). The final concentration of PBMC suspension is 2 x 10^6 cells/mL. The plates are covered with sterile plastic lids, mixed gently and then incubated for 18 to 24 hours at 37°C in a 5% carbon dioxide atmosphere.

Separation

Following incubation the plates are centrifuged for 10 minutes at 1000 rpm (approximately 200 x g) at 4°C. The cell-free culture supernatant is removed with a sterile polypropylene pipet and transferred to sterile polypropylene tubes. Samples are maintained at –30 to -70°C until analysis. The samples are analyzed for interferon (α) by ELISA and for tumor necrosis factor (α) by ELISA or IGEN Assay.

Interferon (α) and Tumor Necrosis Factor (α) Analysis by ELISA

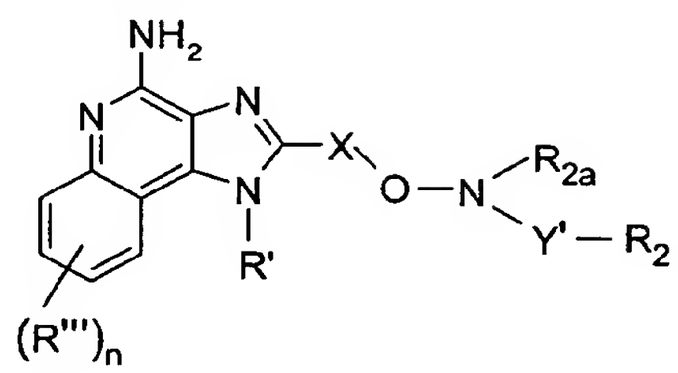
Interferon (α) concentration is determined by ELISA using a Human Multi-Species kit from PBL Biomedical Laboratories, New Brunswick, NJ. Results are expressed in pg/mL.

Tumor necrosis factor (α) (TNF) concentration is determined using ELISA kits available from Biosource International, Camarillo, CA. Alternately, the TNF concentration can be determined by ORIGEN M-Series Immunoassay and read on an IGEN M-8 analyzer from IGEN International, Gaithersburg, MD. The immunoassay uses a human TNF capture and detection antibody pair from Biosource International, Camarillo, CA. Results are expressed in pg/mL.

The complete disclosures of the patents, patent documents, and publications cited herein are incorporated by reference in their entirety as if each were individually incorporated. Various modifications and alterations to this invention will become apparent to those skilled in the art without departing from the scope and spirit of this invention. It should be understood that this invention is not intended to be unduly limited by the illustrative embodiments and examples set forth herein and that such examples and embodiments are presented by way of example only with the scope of the invention intended to be limited only by the claims set forth herein as follows.

WHAT IS CLAIMED IS:

1. A compound of the formula (I):



I

wherein:

X is C_{1-10} alkylene or C_{2-10} alkenylene;

Y' is selected from the group consisting of:

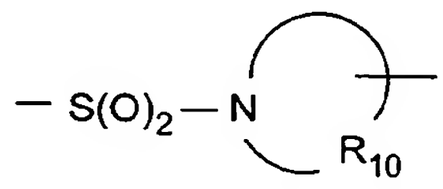
a bond,

-C(O)-,

-C(S)-,

-$S(O)_2$-,

-$S(O)_2$-$N(R_8)$-,



,

-C(O)-O-,

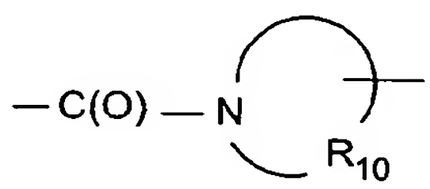
-C(O)-$N(R_8)$-,

-C(S)-$N(R_8)$-,

-C(O)-$N(R_8)$-$S(O)_2$-,

-C(O)-$N(R_8)$-C(O)-,

-C(S)-$N(R_8)$-C(O)-,



,

-C(O)-C(O)-,

-C(O)-C(O)-O-, and

-C(=NH)-$N(R_8)$-;

R_2 and R_{2a} are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxyl,

alkyl,

haloalkyl,

hydroxyalkyl,

alkoxy,

dialkylamino,

$-S(O)_{0-2}$-alkyl,

$-S(O)_{0-2}$-aryl,

$-NH-S(O)_2$-alkyl,

$-NH-S(O)_2$-aryl,

haloalkoxy,

halogen,

nitrile,

nitro,

aryl,

heteroaryl,

heterocyclyl,

aryloxy,

arylalkyleneoxy,

-C(O)-O-alkyl,

-C(O)-N(R_8)$_2$,

-N(R_8)-C(O)-alkyl,

-O-(CO)-alkyl, and

-C(O)-alkyl;

each R_8 is independently selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

R_{10} is C_{3-8} alkylene;

n is 0 to 4;

each R''' is a non-interfering substituent; and

R' is hydrogen or a non-interfering substituent;

or a pharmaceutically acceptable salt thereof.

2. The compound or salt of claim 1 wherein the compound or salt induces the biosynthesis of one or more cytokines.

3. The compound or salt of claim 1 wherein R' is selected from the group consisting of:

-R_4,

-X'-R_4,

-X'-Y-R_4,

-X'-Y-X'-Y-R_4,

-X'-R_5,

-X"-O-NH-Y'-R_1', and

-X"-O-N=C(R_1')(R_1");

wherein:

each X' is independently selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

X" is –CH(R_{13})alkylene or –CH(R_{13})alkenylene;

each Y is independently selected from the group consisting of:

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

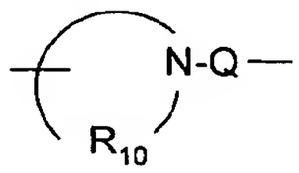
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

$-C(R_6)-N(OR_9)-$,



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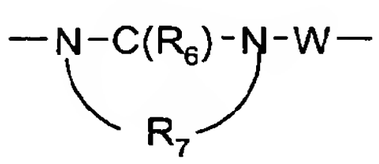

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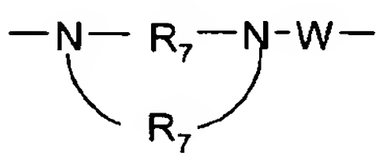

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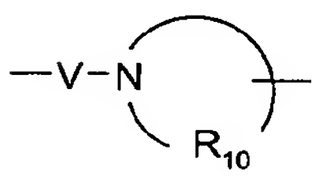

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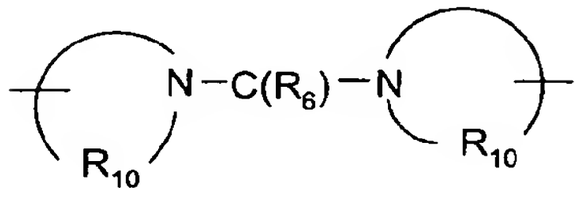
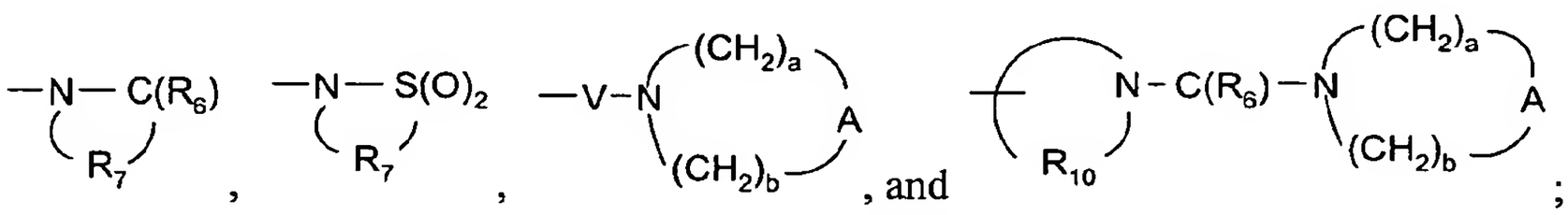


;

each R_4 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy,

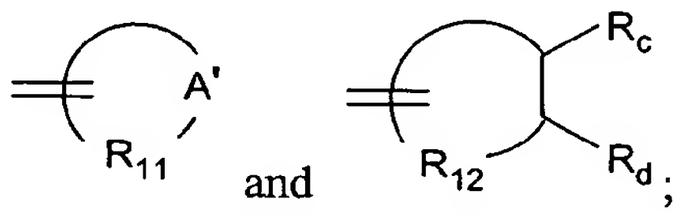
heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

each R_5 is independently selected from the group consisting of



;

R_1' and R_1'' are independently R_2, or R_1' and R_1'' can join together to form a ring system selected from the group consisting of



;

R_c and R_d are independently selected from the group consisting of hydrogen, halogen, hydroxy, alkyl, alkenyl, aryl, haloalkyl, alkoxy, alkylthio, and $-N(R_9)_2$; or R_c and R_d can join to form a fused aryl ring or fused 5-10 membered heteroaryl ring containing one to four hetero atoms;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

each R_8 is independently selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

R_{11} is C_{3-9} alkylene or C_{3-9} alkenylene, optionally interrupted by one hetero atom;

R_{12} is C_{2-7} alkylene or C_{2-7} alkenylene, optionally interrupted by one hetero atom;

R_{13} is selected from the group consisting of hydrogen and alkyl which may be optionally interrupted by one or more -O- groups;

A is selected from the group consisting of $-CH_2-$, -O-, -C(O)-, $-S(O)_{0-2}-$, and $-N(R_4)-$;

A' is selected from the group consisting of -O-, $-S(O)_{0-2}-$, $-N(-Q-R_4)-$. and $-CH_2-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of -C(R_6)-, -O-C(R_6)-, -N(R_8)-C(R_6)-, and -S(O)$_2$-;

W is selected from the group consisting of a bond, -C(O)-, and –S(O)$_2$-; and

a and b are independently integers from 1 to 6 with the proviso that a + b is $\leq$ 7.

4. The compound or salt of claim 1 wherein:

R''' is R or R_3 when n is 1, R or one R and one R_3 when n is 2, or R when n is 3 to 4;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

-N(R_9)$_2$;

R_3 is selected from the group consisting of:

-Z-R_4,

-Z-X'-R_4,

-Z-X'-Y-R_4,

-Z-X'-Y-X'-Y-R_4, and

-Z-X'-R_5;

n is 0 to 4;

Z is a bond or -O-;

each X' is independently selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

each Y is independently selected from the group consisting of:

-S(O)$_{0-2}$-,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

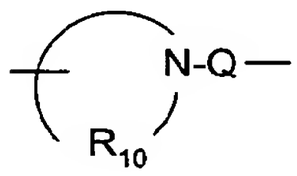
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

$-C(R_6)-N(OR_9)-$,



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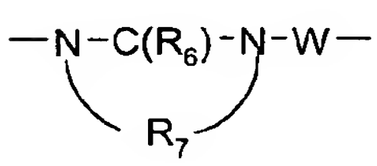

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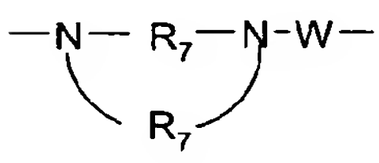

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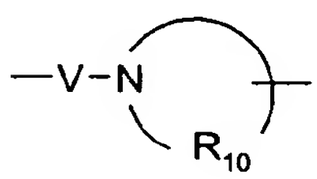

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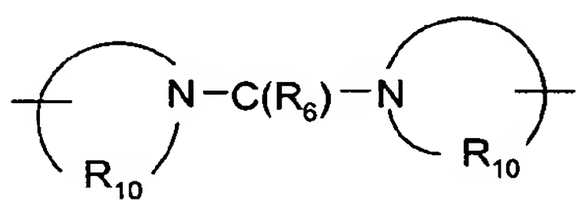
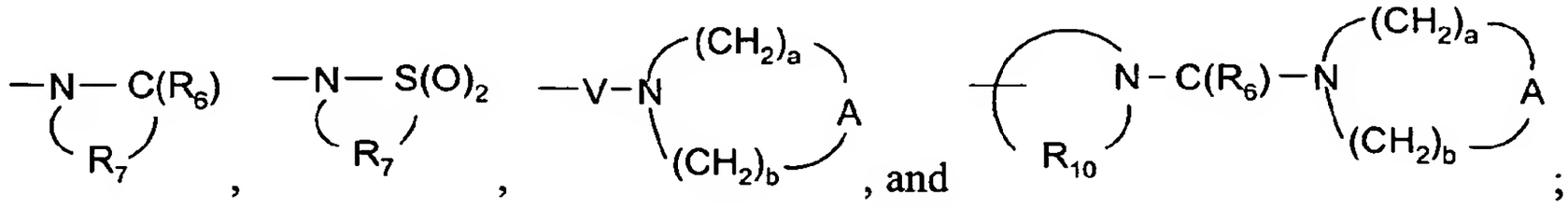


;

each R_4 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino,

(dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

each R_5 is independently selected from the group consisting of



;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

each R_8 is independently selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

each R_9 is independently selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of $-CH_2$-, -O-, -C(O)-, -$S(O)_{0-2}$-, and $-N(R_4)$-;

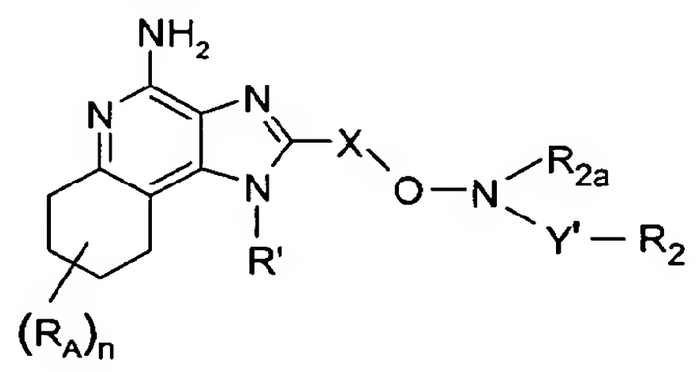
Q is selected from the group consisting of a bond, -$C(R_6)$-, -$C(R_6)$-$C(R_6)$-, -$S(O)_2$-, -$C(R_6)$-$N(R_8)$-W-, -$S(O)_2$-$N(R_8)$-, -$C(R_6)$-O-, and -$C(R_6)$-$N(OR_9)$-;

V is selected from the group consisting of -$C(R_6)$-, -O-$C(R_6)$-, -$N(R_8)$-$C(R_6)$-, and -$S(O)_2$-;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2$-; and

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7.

5. A compound of the formula (II):



II

wherein:

X is C_{1-10} alkylene or C_{2-10} alkenylene;

Y' is selected from the group consisting of:

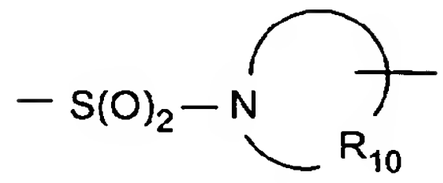
a bond,

-C(O)-,

-C(S)-,

-$S(O)_2$-,

-$S(O)_2$-$N(R_8)$-,



,

-C(O)-O-,

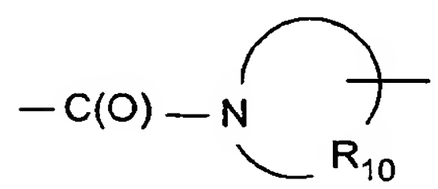
-$C(O)$-$N(R_8)$-,

-$C(S)$-$N(R_8)$-,

-$C(O)$-$N(R_8)$-$S(O)_2$-,

-$C(O)$-$N(R_8)$-$C(O)$-,

-$C(S)$-$N(R_8)$-$C(O)$-,



,

-C(O)-C(O)-,

-C(O)-C(O)-O-, and

-$C(=NH)$-$N(R_8)$-;

R_2 and R_{2a} are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxyl,
alkyl,
haloalkyl,
hydroxyalkyl,
alkoxy,
dialkylamino,
$-S(O)_{0-2}$-alkyl,
$-S(O)_{0-2}$-aryl,
$-NH-S(O)_2$-alkyl,
$-NH-S(O)_2$-aryl,
haloalkoxy,
halogen,
nitrile,
nitro,
aryl,
heteroaryl,
heterocyclyl,
aryloxy,
arylalkyleneoxy;
-C(O)-O-alkyl,
$-C(O)-N(R_8)_2$,
$-N(R_8)-C(O)$-alkyl,
-O-(CO)-alkyl, and
-C(O)-alkyl;

each R_8 is independently selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

R_{10} is C_{3-8} alkylene;

n is 0 to 4;

each R_A is independently selected from the group consisting of halogen, hydroxy, alkyl, alkenyl, haloalkyl, alkoxy, alkylthio, and $-N(R_9)_2$;

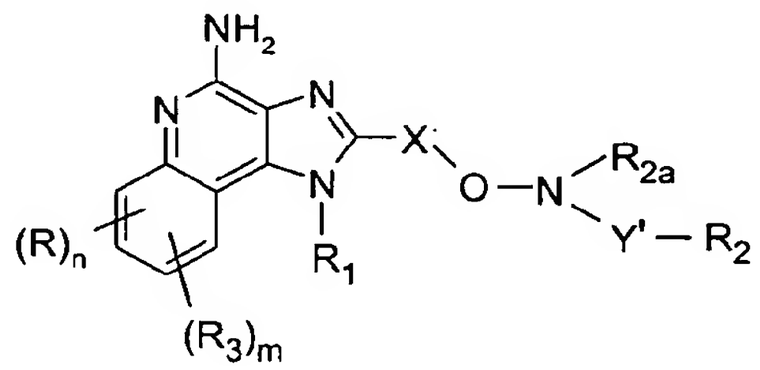
each R_9 is independently selected from the group consisting of hydrogen and alkyl; and

R' is hydrogen or a non-interfering substituent;

or a pharmaceutically acceptable salt thereof.

6. The compound or salt of claim 5 wherein the compound or salt induces the biosynthesis of one or more cytokines.

7. A compound of the formula (Ia):



Ia

wherein:

X is C_{1-10} alkylene or C_{2-10} alkenylene;

Y' is selected from the group consisting of:

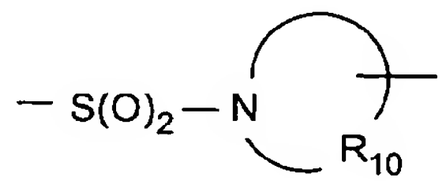
a bond,

-C(O)-,

-C(S)-,

$-S(O)_2-$,

$-S(O)_2-N(R_8)-$,



,

-C(O)-O-,

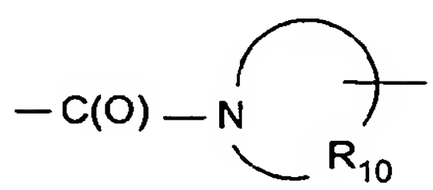
$-C(O)-N(R_8)-$,

$-C(S)-N(R_8)-$,

$-C(O)-N(R_8)-S(O)_2-$,

-C(O)-N(R_8)-C(O)-,

-C(S)-N(R_8)-C(O)-,



,

-C(O)-C(O)-,

-C(O)-C(O)-O-, and

-C(=NH)-N(R_8)-;

R_2 and R_{2a} are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxyl,

alkyl,

haloalkyl,

hydroxyalkyl,

alkoxy,

dialkylamino,

-S(O)$_{0-2}$-alkyl,

-S(O)$_{0-2}$-aryl,

-NH-S(O)$_2$-alkyl,

-NH-S(O)$_2$-aryl,

haloalkoxy,

halogen,

nitrile,

nitro,

aryl,

heteroaryl,

heterocyclyl,

aryloxy,

arylalkyleneoxy,

-C(O)-O-alkyl,

-C(O)-N(R_8)$_2$,

-N(R_8)-C(O)-alkyl,

-O-(CO)-alkyl, and

-C(O)-alkyl;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

-N(R_9)$_2$;

R_1 is selected from the group consisting of:

-R_4,

-X'-R_4,

-X'-Y-R_4,

-X'-Y-X'-Y-R_4,

-X'-R_5,

-X''-O-NH-Y'-R_1', and

-X''-O-N=C(R_1')(R_1'');

R_3 is selected from the group consisting of:

-Z-R_4,

-Z-X'-R_4,

-Z-X'-Y-R_4,

-Z-X'-Y-X'-Y-R_4, and

-Z-X'-R_5;

n is 0 to 4;

m is 0 or 1; with the proviso that when m is 1, then n is 0 or 1;

each X' is independently selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

X" is –CH(R_{13})alkylene or –CH(R_{13})alkenylene;

each Y is independently selected from the group consisting of:

-$S(O)_{0-2}$-,

-$S(O)_2$-N(R_8)-,

-C(R_6)-,

-C(R_6)-O-,

-O-C(R_6)-,

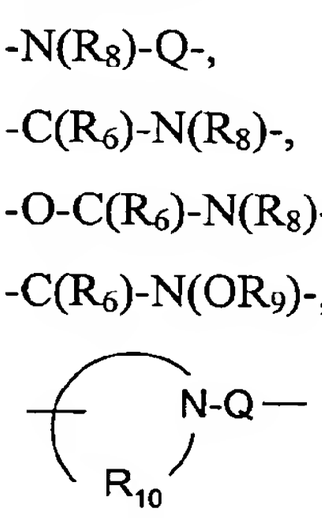
-O-C(O)-O-,

-N(R_8)-Q-,

-C(R_6)-N(R_8)-,

-O-C(R_6)-N(R_8)-,

-C(R_6)-N(OR_9)-,



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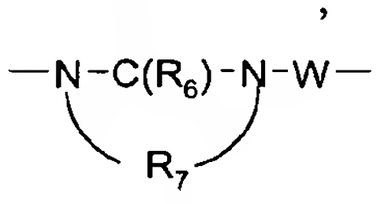

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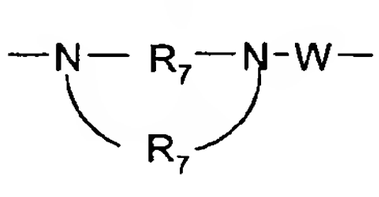

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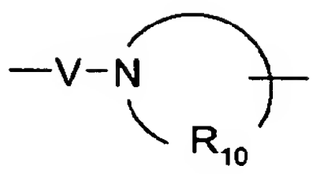
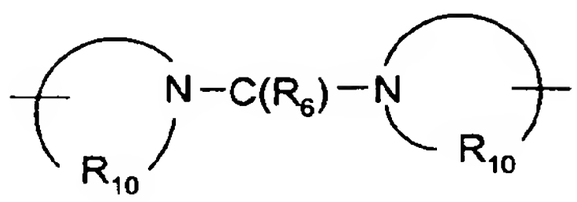
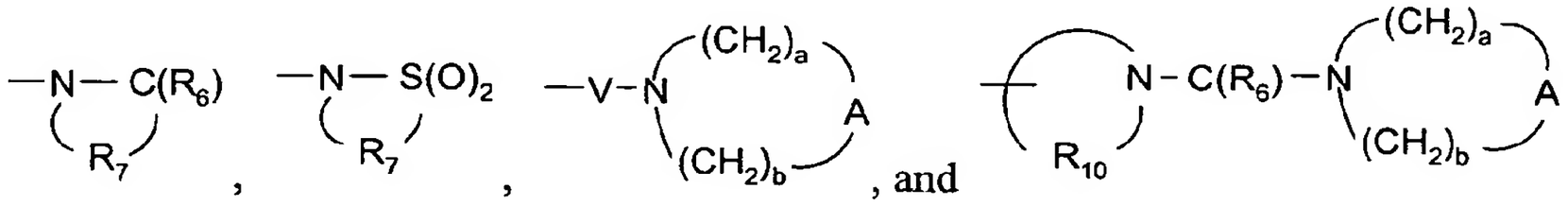

, and


;

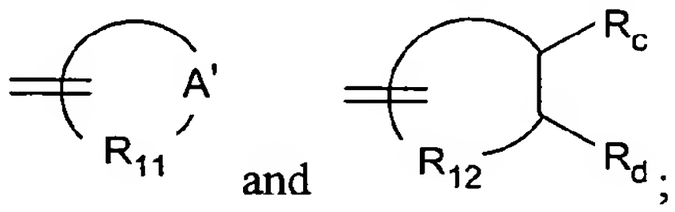
Z is a bond or -O-;

each R_4 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

each R_5 is independently selected from the group consisting of


;

R_1', and R_1'' are independently the same as R_2, or R_1' and R_1'' can join together to form a ring system selected from the group consisting of


;

R_c and R_d are independently selected from the group consisting of hydrogen, halogen, hydroxy, alkyl, alkenyl, aryl, haloalkyl, alkoxy, alkylthio, and $-N(R_9)_2$; or R_c and R_d can join to form a fused aryl ring or fused 5-10 membered heteroaryl ring containing one to four hetero atoms;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

each R_8 is independently selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

each R_9 is independently selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

R_{11} is C_{3-9} alkylene or C_{3-9} alkenylene, optionally interrupted by one hetero atom;

R_{12} is C_{2-7} alkylene or C_{2-7} alkenylene, optionally interrupted by one hetero atom;

R_{13} is selected from the group consisting of hydrogen and alkyl which may be optionally interrupted by one or more -O- groups;

A is selected from the group consisting of $-CH_2-$, -O-, -C(O)-, $-S(O)_{0-2}-$, and $-N(R_4)-$;

A' is selected from the group consisting of -O-, $-S(O)_{0-2}-$, $-N(-Q-R_4)-$. and $-CH_2-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

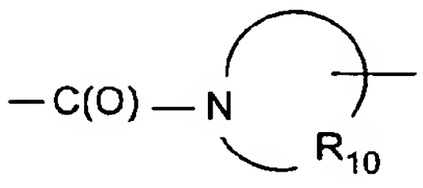
W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$; and

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

or a pharmaceutically acceptable salt thereof.

8. The compound or salt of claim 7 wherein X is C_{1-4} alkylene.

9. The compound or salt of claim 7 wherein Y' is selected from the group consisting of a bond, -C(O)-, -C(O)-O-, $-S(O)_2-$, $-S(O)_2-N(R_8)-$, $-C(O)-N(R_8)-$, $-C(O)-N(R_8)-C(O)-$, and



10. The compound or salt of claim 7 wherein R_2 and R_{2a} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, aryl, heteroaryl, wherein the alkyl, alkenyl, aryl, and heteroaryl are each optionally substituted with one or more substitutents

selected from the group consisting of C_{1-10} alkyl, aryl, heteroaryl, C_{1-10} alkoxy, -O-C(O)-C_{1-10} alkyl, -C(O)-O-C_{1-10} alkyl, halogen, and nitrile.

11. The compound or salt of claim 7 wherein R_{2a} is hydrogen.

12. The compound or salt of claim 7 wherein R_2 is alkyl or substituted alkyl, and R_{2a} is hydrogen.

13. The compound or salt of claim 7 wherein R_2 is alkenyl or substituted alkenyl, and R_{2a} is hydrogen.

14. The compound or salt of claim 7 wherein R_2 is aryl, arylalkylenyl, substituted aryl, or substituted arylalkylenyl, and R_{2a} is hydrogen.

15. The compound or salt of claim 7 wherein R_2 is heteroaryl , heteroarylalkylenyl, substituted heteroaryl, or substituted heteroarylalkylenyl, and R_{2a} is hydrogen.

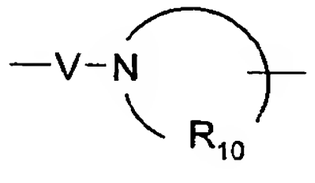
16. The compound or salt of claim 7 wherein R_2 is heterocyclyl, heterocyclylalkylenyl, substituted heterocyclyl, or substituted heterocyclylalkylenyl, and R_{2a} is hydrogen.

17. The compound or salt of claim 7 wherein R_2 is selected from the group consisting of methyl, (ethoxycarbonyl)methyl, ethyl, cyclopropyl, cyclopropylmethyl, 2-(ethoxycarbonyl)cyclopropylmethyl, propyl, butyl, 2-methylpropyl, *tert*-butyl, 3-methylbutyl, 2,2-dimethylpropyl, cyclopentyl, 2-cyclopentylethyl, furyl, fur-3-ylmethyl, furfuryl, furfurylmethyl, cyclohexyl, tetrahydrofuranyl, tetrahydrofuran-3-ylmethyl, 2-(methylthio)ethyl, 2-(methylthio)propyl, phenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2,6-dimethoxyphenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-cyanophenyl, 3-cyanophenyl, 4-cyanophenyl, 4-(dimethylamino)phenyl, 3-hydroxy-4-methoxyphenyl, 4-acetamidophenyl, 4-(methoxycarbonyl)phenyl, 4-(trifluoromethyl)phenyl, biphenyl, benzyl, 2-methylbenzyl, 3-

methylbenzyl, 4-methylbenzyl, 2-fluorobenzyl, 3-fluorobenzyl, 4-fluorobenzyl, 2-chlorobenzyl, 3-chlorobenzyl, 4-chlorobenzyl, 2-cyanobenzyl, 3-cyanobenzyl, 4-cyanobenzyl, 2-methoxybenzyl, 3-methoxybenzyl, 4-methoxybenzyl, 4-dimethylaminobenzyl, 3-hydroxy-4-methoxybenzyl, 4-acetamidobenzyl, 4-(methoxycarbonyl)benzyl, 4-(trifluoromethyl)benzyl, 1-phenylethyl, 2-phenylethyl, 2-phenylpropyl, 3-phenylpropyl, 2-phenylethenyl, phenoxymethyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyridylmethyl, 3-pyridylmethyl, 4-pyridylmethy, 1-methylpyrrol-2-yl, 1-methylpyrrol-2-ylmethyl, 1-methylimidazol-2-yl, 1-methylimidazol-2-ylmethyl, 1-methylimidazol-4-yl, 1-methylimidazol-4-ylmethyl, 3-cyclohexen-1-yl, 3-cyclohexen-1-ylmethyl, 3,4-dihydro-2*H*-pyran-2-yl, 3,4-dihydro-2*H*-pyran-2-ylmethyl, 1-methylpiperidin-4-yl, 1-acetylpiperidin-4-yl, 1-benzylpiperidin-4-yl, 2-thienyl, 3-thienyl, thien-2-ylmethyl, thiazol-2-yl, thiazol-2-ylmethyl, 5-isoxazolyl, 5-isoxazolylmethyl, quinolin-2-yl, quinolin-2-ylmethyl, and pyrrolidinyl; and R_{2a} is hydrogen.

18. The compound or salt of claim 7 wherein R_1 is selected from the group consisting of

alkyl, arylalkylenyl, aryloxyalkylenyl, hydroxyalkyl, alkylsulfonylalkylenyl, -X'-Y-R_4, and -X'-R_5; wherein X' is alkylene; Y is -N(R_8)-C(O)-, -N(R_8)-S(O)$_2$-, -N(R_8)-S(O)$_2$-N(R_8)-, -N(R_8)-C(O)-N(R_8)-, -N(R_8)-C(O)-N(R_8)-C(O)-,



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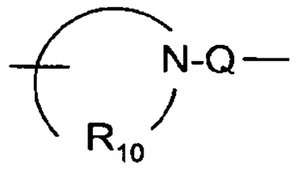
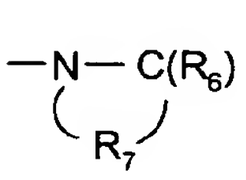


; R_4 is hydrogen, alkyl, alkenyl, aryl, or heteroaryl; and R_5 is



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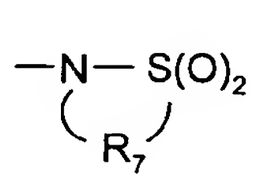

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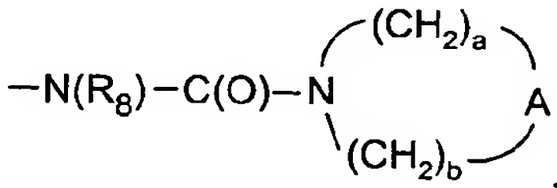
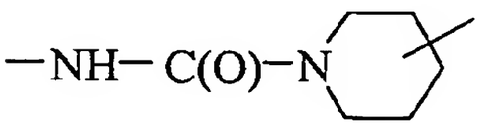


.

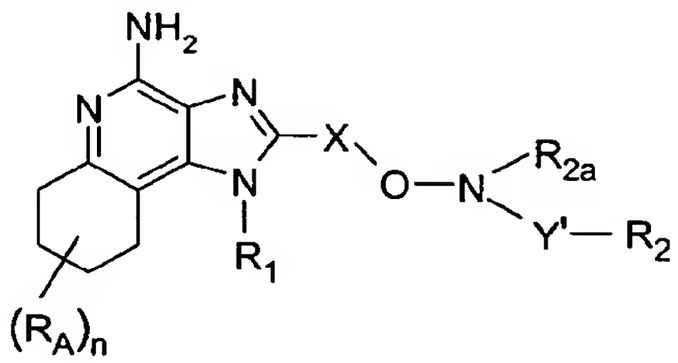
19. The compound or salt of claim 18 wherein R_1 is 2-methylpropyl or –X'-Y-R_4; X' is ethylene, propylene, or butylene; Y is -NH-C(O)-, -NH-S(O)$_2$-, -NH-S(O)$_2$-N(R_8)-, -NH-C(O)-N(R_8)-, -NH-C(O)-NH-C(O)-, or



; and R_8 is hydrogen or methyl.

20. The compound or salt of claim 7 wherein n and m are 0.

21. A compound of the formula (IIa):



IIa

wherein:

X is C_{1-10} alkylene or C_{2-10} alkenylene;

Y' is selected from the group consisting of:

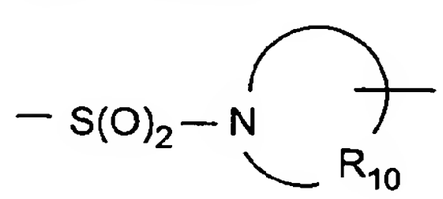
a bond,

-C(O)-,

-C(S)-,

-$S(O)_2$-,

-$S(O)_2$-N(R_8)-,



,

-C(O)-O-,

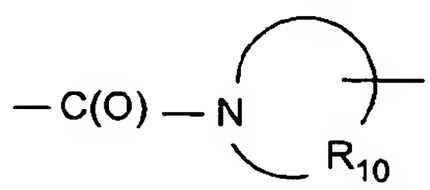
-C(O)-N(R_8)-,

-C(S)-N(R_8)-,

-C(O)-N(R_8)-$S(O)_2$-,

-C(O)-N(R_8)-C(O)-,

-C(S)-N(R_8)-C(O)-,



,

-C(O)-C(O)-,

-C(O)-C(O)-O-, and

-C(=NH)-N(R_8)-;

R_2 and R_{2a} are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxyl,

alkyl,

haloalkyl,

hydroxyalkyl,

alkoxy,

dialkylamino,

-$S(O)_{0-2}$-alkyl,

-$S(O)_{0-2}$-aryl,

-NH-$S(O)_2$-alkyl,

-NH-$S(O)_2$-aryl,

haloalkoxy,

halogen,

nitrile,

nitro,

aryl,

heteroaryl,

heterocyclyl,

aryloxy,

arylalkyleneoxy;

-C(O)-O-alkyl,

-C(O)-N(R_8)$_2$,

-N(R_8)-C(O)-alkyl,

-O-(CO)-alkyl, and

-C(O)-alkyl;

R_A is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

-N(R_9)$_2$;

n is 0 to 4;

R_1 is selected from the group consisting of:

-R_4,

-X'-R_4,

-X'-Y-R_4,

-X'-Y-X'-Y-R_4,

-X'-R_5,

-X"-O-NH-Y'-R_1', and

-X"-O-N=C(R_1')(R_1");

each X' is independently selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

X" is –CH(R_{13})alkylene or –CH(R_{13})alkenylene;

each Y is independently selected from the group consisting of:

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

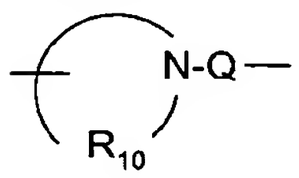
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

$-C(R_6)-N(OR_9)-$,



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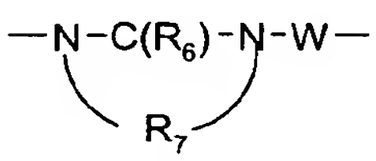

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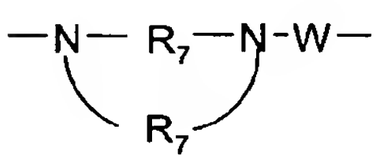

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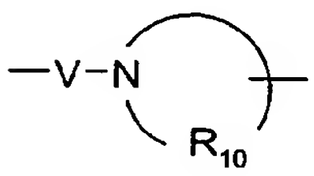

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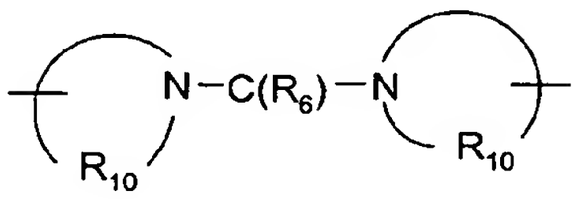

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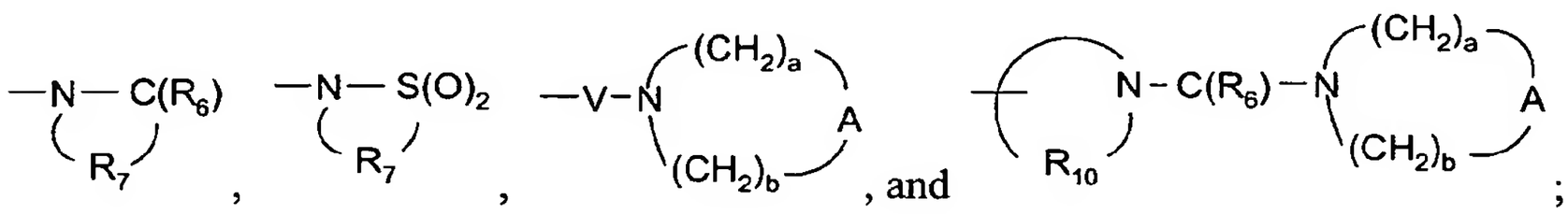
each R_4 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino,

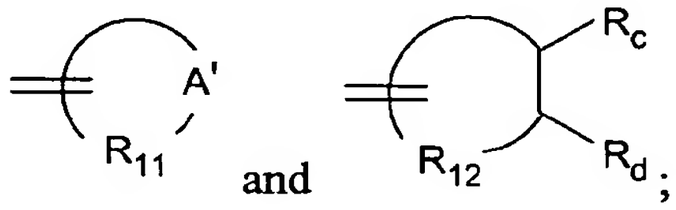
(dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

each R_5 is independently selected from the group consisting of



;

R_1', and R_1'' are independently R_2, or R_1' and R_1'' can join together to form a ring system selected from the group consisting of



;

R_c and R_d are independently selected from the group consisting of hydrogen, halogen, hydroxy, alkyl, alkenyl, aryl, haloalkyl, alkoxy, alkylthio, and $-N(R_9)_2$; or R_c and R_d can join to form a fused aryl ring or fused 5-10 membered heteroaryl ring containing one to four hetero atoms;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

each R_8 is independently selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

each R_9 is independently selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

R_{11} is C_{3-9} alkylene or C_{3-9} alkenylene, optionally interrupted by one hetero atom;

R_{12} is C_{2-7} alkylene or C_{2-7} alkenylene, optionally interrupted by one hetero atom;

R_{13} is selected from the group consisting of hydrogen and alkyl which may be optionally interrupted by one or more -O- groups;

A is selected from the group consisting of $-CH_2-$, -O-, -C(O)-, $-S(O)_{0-2}-$, and $-N(R_4)-$;

A' is selected from the group consisting of -O-, $-S(O)_{0-2}-$, -N(-Q-R_4)-. and $-CH_2-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and

$-S(O)_2-$;

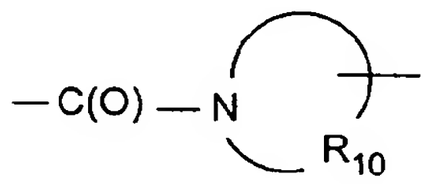
W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$; and

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

or a pharmaceutically acceptable salt thereof.

22. The compound or salt of claim 21 wherein X is C_{1-4} alkylene.

23. The compound or salt of claim 21 wherein Y' is selected from the group consisting of a bond, -C(O)-, -C(O)-O-, $-S(O)_2-$, $-S(O)_2-N(R_8)-$, $-C(O)-N(R_8)-$, $-C(O)-N(R_8)-C(O)-$, and



24. The compound or salt of claim 21 wherein R_2 and R_{2a} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, aryl, heteroaryl, wherein the alkyl, alkenyl, aryl, and heteroaryl are each optionally substituted with one or more substitutents selected from the group consisting of C_{1-10} alkyl, aryl, heteroaryl, C_{1-10} alkoxy, -O-C(O)-C_{1-10} alkyl, -C(O)-O-C_{1-10} alkyl, halogen, and nitrile.

25. The compound or salt of claim 21 wherein R_{2a} is hydrogen.

26. The compound or salt of claim 21 wherein R_2 is alkyl or substituted alkyl, and R_{2a} is hydrogen.

27. The compound or salt of claim 21 wherein R_2 is alkenyl or substituted alkenyl, and R_{2a} is hydrogen.

28. The compound or salt of claim 21 wherein R_2 is aryl, arylalkylenyl, substituted aryl, or substituted arylalkylenyl, and R_{2a} is hydrogen.

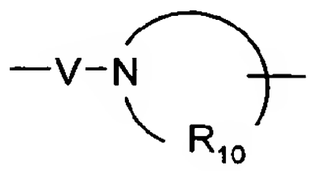
29. The compound or salt of claim 21 wherein R_2 is heteroaryl , heteroarylalkylenyl, substituted heteroaryl, or substituted heteroarylalkylenyl, and R_{2a} is hydrogen.

30. The compound or salt of claim 21 wherein R_2 is heterocyclyl, heterocyclylalkylenyl, substituted heterocyclyl, or substituted heterocyclylalkylenyl, and R_{2a} is hydrogen.

31. The compound or salt of claim 21 wherein R_2 is selected from the group consisting of methyl, (ethoxycarbonyl)methyl, ethyl, cyclopropyl, cyclopropylmethyl, 2-(ethoxycarbonyl)cyclopropylmethyl, propyl, butyl, 2-methylpropyl, *tert*-butyl, 3-methylbutyl, 2,2-dimethylpropyl, cyclopentyl, 2-cyclopentylethyl, furyl, fur-3-ylmethyl, furfuryl, furfurylmethyl, cyclohexyl, tetrahydrofuranyl, tetrahydrofuran-3-ylmethyl, 2-(methylthio)ethyl, 2-(methylthio)propyl, phenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2,6-dimethoxyphenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-cyanophenyl, 3-cyanophenyl, 4-cyanophenyl, 4-(dimethylamino)phenyl, 3-hydroxy-4-methoxyphenyl, 4-acetamidophenyl, 4-(methoxycarbonyl)phenyl, 4-(trifluoromethyl)phenyl, biphenyl, benzyl, 2-methylbenzyl, 3-methylbenzyl, 4-methylbenzyl, 2-fluorobenzyl, 3-fluorobenzyl, 4-fluorobenzyl, 2-chlorobenzyl, 3-chlorobenzyl, 4-chlorobenzyl, 2-cyanobenzyl, 3-cyanobenzyl, 4-cyanobenzyl, 2-methoxybenzyl, 3-methoxybenzyl, 4-methoxybenzyl, 4-dimethylaminobenzyl, 3-hydroxy-4-methoxybenzyl, 4-acetamidobenzyl, 4-(methoxycarbonyl)benzyl, 4-(trifluoromethyl)benzyl, 1-phenylethyl, 2-phenylethyl, 2-phenylpropyl, 3-phenylpropyl, 2-phenylethenyl, phenoxymethyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyridylmethyl, 3-pyridylmethyl, 4-pyridylmethy, 1-methylpyrrol-2-yl, 1-methylpyrrol-2-ylmethyl, 1-methylimidazol-2-yl, 1-methylimidazol-2-ylmethyl, 1-methylimidazol-4-yl, 1-methylimidazol-4-ylmethyl, 3-cyclohexen-1-yl, 3-cyclohexen-1-ylmethyl, 3,4-dihydro-2*H*-pyran-2-yl, 3,4-dihydro-2*H*-pyran-2-ylmethyl, 1-methylpiperidin-4-yl, 1-acetylpiperidin-4-yl, 1-benzylpiperidin-4-yl, 2-thienyl, 3-thienyl, thien-2-ylmethyl, thiazol-2-yl, thiazol-2-ylmethyl, 5-isoxazolyl, 5-isoxazolylmethyl, quinolin-2-yl, quinolin-2-ylmethyl, and pyrrolidinyl; and R_{2a} is hydrogen.

32. The compound or salt of claim 21 wherein R_1 is selected from the group consisting of

alkyl, arylalkylenyl, aryloxyalkylenyl, hydroxyalkyl, alkylsulfonylalkylenyl, -X'-Y-R_4, and -X'-R_5; wherein X' is alkylene; Y is -N(R_8)-C(O)-, -N(R_8)-S(O)$_2$-, -N(R_8)-S(O)$_2$-N(R_8)-, -N(R_8)-C(O)-N(R_8)-, -N(R_8)-C(O)-N(R_8)-C(O)-,



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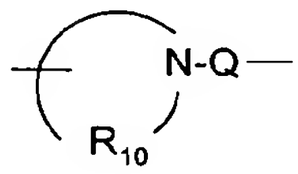
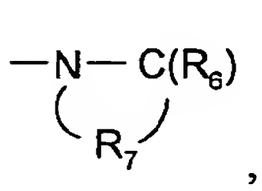


; R_4 is hydrogen, alkyl, alkenyl, aryl, or heteroaryl; and R_5 is



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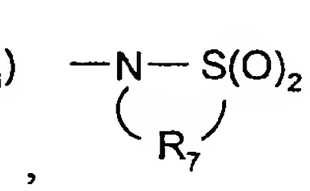

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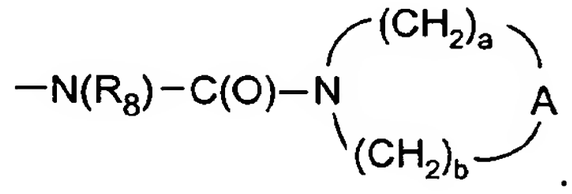

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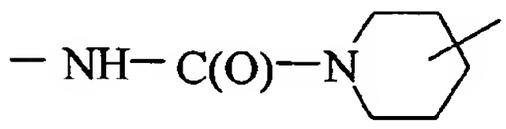
33. The compound or salt of claim 32 wherein R_1 is 2-methylpropyl or –X'-Y-R_4; X' is ethylene, propylene, or butylene; Y is -NH-C(O)-, -NH-S(O)$_2$-, -NH-S(O)$_2$-N(R_8)-, -NH-C(O)-N(R_8)-, -NH-C(O)-NH-C(O)-, or



; and R_8 is hydrogen or methyl.

34. The compound or salt of claim 21 wherein n is 0.

35. A pharmaceutical composition comprising a therapeutically effective amount of a compound or salt of claim 1 in combination with a pharmaceutically acceptable carrier.

36. A pharmaceutical composition comprising a therapeutically effective amount of a compound or salt of claim 5 in combination with a pharmaceutically acceptable carrier.

37. A pharmaceutical composition comprising a therapeutically effective amount of a compound or salt of claim 7 in combination with a pharmaceutically acceptable carrier.

38. A pharmaceutical composition comprising a therapeutically effective amount of a compound or salt of claim 21 in combination with a pharmaceutically acceptable carrier.

39. A method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or salt of claim 1 to the animal.

40. A method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or salt of claim 5 to the animal.

41. A method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or salt of claim 7 to the animal.

42. A method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or salt of claim 21 to the animal.

43. A method of treating a viral disease in an animal in need thereof comprising administering a therapeutically effective amount of a compound or salt of claim 1 to the animal.

44. A method of treating a viral disease in an animal in need thereof comprising administering a therapeutically effective amount of a compound or salt of claim 5 to the animal.

45. A method of treating a viral disease in an animal in need thereof comprising administering a therapeutically effective amount of a compound or salt of claim 7 to the animal.

46. A method of treating a viral disease in an animal in need thereof comprising administering a therapeutically effective amount of a compound or salt of claim 21 to the animal.

47. A method of treating a neoplastic disease in an animal in need thereof comprising administering a therapeutically effective amount of a compound or salt of claim 1 to the animal.

48. A method of treating a neoplastic disease in an animal in need thereof comprising administering a therapeutically effective amount of a compound of or salt claim 5 to the animal.

49. A method of treating a neoplastic disease in an animal in need thereof comprising administering a therapeutically effective amount of a compound of or salt claim 7 to the animal.

50. A method of treating a neoplastic disease in an animal in need thereof comprising administering a therapeutically effective amount of a compound or salt of claim 21 to the animal.

HYDROXYLAMINE SUBSTITUTED IMIDAZOQUINOLINES

ABSTRACT OF THE DISCLOSURE

Imidazoquinoline compounds with a hydroxylamine substituent at the 2-position, pharmaceutical compositions containing the compounds, intermediates, and methods of use of these compounds as immunomodulators, for inducing cytokine biosynthesis in animals and in the treatment of diseases including viral and neoplastic diseases are disclosed.